RADIUM THERAPEUTICS

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PREFACE

In this little book I have tried to place before the profession a brief and clear account of the action and uses of radium and its rays. In the present limited state of our knowledge of the therapeutics of this substance and with new uses for it arising every few weeks, I have endeavoured to distinguish between ascertained facts and results which have not been definitely proved. This is my excuse for the comparatively scanty information furnished on some points.

I tender my most grateful thanks to Professor Makower for kindly reading through and revising Chapter I.; to Dr. Knox and Mr. C. E. S. Phillips for their great assistance in reading through the manuscript and suggesting various alterations and improvements; to Dr. William Hill for hints on the pages on the œsophagus and for his kind loan of the blocks for some of the illustrations; and to Miss B. Temple Orme for kindly reading through the proofs.

The beautiful photo-micrographs in Chapter III. were kindly made for me by my friend, Mr. H. Lloyd Hind of Burton-on-Trent, from sections in my possession; to him also I tender this expression of my gratitude.

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RADIUM THERAPEUTICS

CHAPTER I

INTRODUCTORY

It is essential, in order to understand the principles of the different methods of application of radium and the reasons for the employment of these methods in various diseases, to have a very clear outline of the physics and chemistry of this substance. The actual mechanism of its physiological action is often most obscure, but without a slight knowledge of the various products that constitute "radium" the obscurity would become absolute darkness.

Radium (symbol, Ra) is a metal which was first isolated from its compounds by Madame Curie in 1910, though its existence had been discovered some dozen years before by Monsieur and Madame Curie following some work by Becquerel on radio-activity.

Its atomic weight is 226·5, and it falls into the same group in the periodic table as calcium, strontium, and barium, which it resembles in its chemical reactions. It is a bright white metal which rapidly tarnishes if exposed to the air and decomposes water. It combines powerfully with the halogens and acid radicles, forming stable compounds the chemical behaviour of which

resembles that of salts of the alkaline earths. In one way, however, radium differs very materially from the other alkaline earth metals, and that is in possessing the property of radio-activity; all its compounds have this and in proportion to the amount of the metal they contain. With this property is associated the production of helium, which will be discussed presently.

By radio-activity we mean the property of certain substances of giving out spontaneously rays which will affect a photographic plate, cause florescence in certain substances, and render air a conductor of electricity by "ionising" it. In the case of radium, the metal itself gives out rays but it also gives off continuously a radio-active gas called the "emanation."[1] The rays from radium itself have been shown to be particles the size of atoms carrying a positive charge and are known as the α-particles: it seems probable that they are due to an actual breaking down of the radium atom, the emanation being the one product, with an atomic weight little below that of radium, and positively charged atoms of helium, with an atomic weight of 4, the other. The atomic weight of the emanation is of course 222·5 (226·5 minus 4), owing to the atom of helium the radium loses: its production goes on at a constant rate, the amount produced depending solely on the amount of metallic radium. It is estimated that half the radium will have decayed in two thousand years, half the remainder will have decayed in another two thousand, and so on. The greater part of the emanation can be obtained from a solution of a radium

[1] Sir William Ramsay has given the name "niton" to this gas.

salt by bubbling air through it or by pumping the gas out of the solution by a vacuum pump. Water, in contact with an insoluble radium salt, will also take a certain quantity of emanation into solution, though a considerable part will remain locked up in the salt. The emanation can be obtained in a state of purity either by heating the chloride to redness and condensing the emanation by means of liquid air, or by extracting the gases from a radium solution kept in vacuum, exploding the oxygen and hydrogen [1] formed by the decomposition of the water by the radium dissolved in it, drying the resulting gas and condensing the emanation from this.

The emanation, like the parent substance, gives off α-rays, and again there is a formation of helium and of another substance of high atomic weight, this time a solid, known as radium A. This breaking down, like the formation of the emanation, goes on at a constant rate. If the emanation is separated from the radium, half will be converted into radium A in 3·85 days, half the remainder in a further 3·85 days, and so on. Radium A again breaks down, giving off α-particles and is transformed into radium B, which is then further converted into radium C; this last transformation, however, is associated with the production of different particles known as β-rays, which have a negative charge and are only $\frac{1}{1700}$th the size of the α-particles. It has lately been shown that radium itself also gives off some β-particles. From radium C there are both α- and β-rays, and, in addition, another radiation known as γ-rays. There is still considerable doubt as to the nature of these,

[1] An excess of hydrogen occurs for some unknown reason.

one theory holding that they are not particles at all, but ether disturbances similar to X-rays: on the contrary, Bragg holds the view that both they and X-rays are corpuscular. These γ-rays are generally, perhaps always, associated with β-rays, but whether the converse is true is not quite certain. The next substance, radium D, was at one time thought to give off no rays which could be detected by the ordinary means, but has now been shown to emit β-rays of comparatively low velocity. Further transformation products are radium E and radium F. The last is identical with polonium and gives off α-rays only. What is left after this is not yet known, but it is believed to be lead. It is extremely likely that radium itself is derived from the decay of another radio-active substance, uranium, there being at least one intermediate body, ionium. One fact very strongly in favour of this is that all uranium ores contain radium approximately in a definite proportion to the amount of uranium present. The formation of radium from ionium has been proved.

These changes are shown in the following table :—

	Time to fall to half value.	Radiations.
Radium . . .	About 2000 years.	α and β.
Emanation . .	3·85 days.	α.
Radium A. . .	3 minutes.	α.
Radium B. . .	26·8 minutes.	β and γ
Radium C. . .	19·5 minutes.	α, β, and γ.
(Radium C^2 . .	1·4 minutes.	β).*
Radium D . .	16·5 years.	Slow β.
Radium E. . .	5 days.	β and γ.
Radium F. . .	136 days.	α.

* Occurs in small quantities and is probably a branch product.

If radium is sealed up until the amount of the transformation products, which are formed, is counterbalanced by the amount which decays, it is said to be in equilibrium. Its activity, especially that of the β- and γ-rays, is then mostly due to the emanation and its subsequent products: radium itself accounts for 25 per cent. of the total α-ray activity. The emanation can therefore be separated from the radium and used for therapeutic purposes. Owing to the slow decay of radium D, it accumulates and there is a very slight increase in activity of a sealed-up radium salt which goes on for over two hundred years before equilibrium is established.

The unit of emanation is the "curie," and is the amount in equilibrium with one gram of pure radium (metal). A millicurie is the thousandth part of this.

THE RADIATIONS

The α-Radiations

These, as has been mentioned, are atoms and carry a positive charge. They travel with a great initial velocity, but owing to their comparatively large mass they are easily stopped, 7 cms. of air, $\frac{1}{20}$ mm. of aluminium, or a sheet of thick note-paper being sufficient to reduce the speed of the most penetrating of them to a sufficient extent to prevent their presence being recognised. In most forms of apparatus these radiations are absorbed completely or to a large extent by the vessel containing or varnish covering the radium salt. They are deflected by a very strong magnetic field, owing to the positive charge they carry. The distance the α-particles will penetrate a

given gas and still continue to ionise it is known as their range for that gas. The ranges in air of the α-particles from radium, the emanation, radium A and radium C respectively, are 3·50 cms., 4·35 cms., 4·82 cms., and 7·08 cms.

The β-Radiations

The β-rays are also particles but of much smaller size, and besides being projected with about ten times the velocity of the α-rays, their small mass helps to make them much more penetrating: the velocity of the fastest of them is almost equal to that of light. As they are negatively charged they are deflected by a magnet in the opposite direction to the α-rays. They have a varying power of penetration; $\frac{1}{10}$th mm. of lead will cut off quite a large proportion, but some of the rays will get through 1 or 2 mm. of lead. There is a strong resemblance between them and the cathode rays of an X-ray tube. The different metals cut off an amount of β-rays that varies with their specific gravity.

The γ-Radiations

The γ-rays have enormous penetrating power and some will, in fact, go through a foot or more of lead while an inch only cuts them down to half. They were believed to be ether vibrations, though this had not yet been proved, and Bragg's hypothesis that they are corpuscular has many adherents: they are not deflected by a magnet, and they strongly resemble X-rays but are very much more penetrating.

Until recently it was believed that none of these rays are either reflected or refracted, but when the

β- or γ-rays pass through any substance they cause it to give off secondary radiations with properties which are to some degree dependent on the substance used and which may differ from the primary radiations both in absorption and nature of the rays; thus, when the γ-rays strike a mass of lead, this metal gives out rays similar to both the β and γ, but without their great penetrating power; roughly, the secondary radiation from lead is about half absorbed by $\frac{1}{4}$ mm. of aluminium, and so is equivalent to very soft X-rays.

All these radiations possess the power of ionising gases and so discharging a charged electroscope; they also have the power of accelerating chemical changes. For instance, they will cause to oxidise an aluminium vessel in which the radium is contained, whereas in the ordinary way this metal is hardly affected by the air.

It will be seen that if radium be sealed up in a glass tube the α-particles do not get out unless the walls of the tube are exceedingly thin, while the β-particles do; so, if the α-particles are retained, the radium in the tube will, if the insulation be good enough, gradually acquire a strong positive charge. If, now, it is required to open this tube and a file mark is made on the glass, a spark may pass from the radium inside to the file, and as the radium has caused the decomposition of the water vapour in contact with it into oxygen and hydrogen there will be a small explosion which will scatter the precious salt. This actually happened to two small tubes belonging to the author, and Abbé of America has recorded the spontaneous explosion of a glass tube, probably due to a similar cause. The danger can be

obviated by sealing a platinum wire into the glass tube in which the radium is to be placed.

The Separation of the Radiations

The α-radiations can be isolated by using radium F, also known as polonium, which gives off α-particles

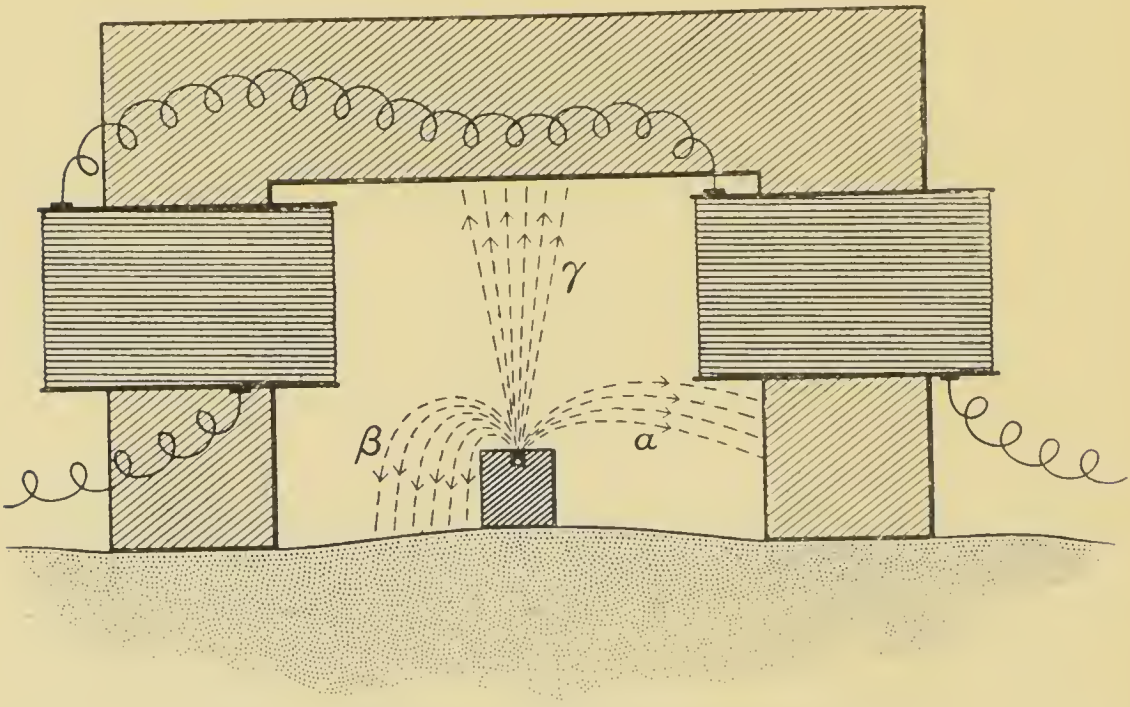


Fig. 1.—Diagram of Apparatus for Isolation of β rays.

only. Fortunately, this is separated readily by chemical means from the rest of the radium transformation products. It has not yet been employed therapeutically.

The β-rays cannot be completely separated from the γ. If a thin filter, such as $\frac{1}{10}$th mm. of aluminium, be employed to cut off the α-rays only, a mixture of β- and γ-rays is left in which the β are in sufficient amount to dominate the therapeutic result. In such a

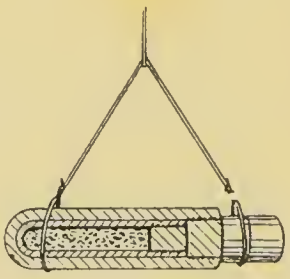
mixture the total heating effect of the γ-radiation is greater than that of the β: the statements of some French writers that the β-rays predominate in the proportion of 10 to 1 is due to the fact that they have measured the ionisation caused by the rays and have used for this purpose an ionisation chamber which allowed the γ-rays to pass through unabsorbed. For experimental purposes a preponderance of β-rays might be obtained by using a powerful magnet to deflect the β-particles having the radium in a well in a thick lead case (Fig. 1).

The γ-rays can be isolated by using a filter of metal which is sufficient to cut out all the β-particles. Two millimetres of lead is enough to effect this, and, of course, also absorbs all the α-particles. Outside this must be used some substance of low atomic weight to absorb the secondary radiations given off by the metallic filter.

Secondary Radiations

When either the β- or the γ-rays strike a block of metal or other substance of high density they cause this to give off what are known as secondary radiations. It is not proposed to enter into the nature of these, but it will suffice to say they are less penetrating than the radiation which produces them. Fig. 2 illustrates a simple experiment to demonstrate the presence of these and their absorbability. A photographic plate wrapped in light-proof paper was placed film downwards on a lead cylinder closed at the farther end (half the case used for carrying one of the radium tubes), a triangle of aluminium 0·25 mm.

thick being placed between them to test the absorbability of the radiation. A tube containing radium, surrounded by a platinum filter, 2 mm. thick, was then suspended over the back of the plate for a few minutes. It will be seen that, though the plate is slightly affected by the radium, the secondary radiations from the circle of lead



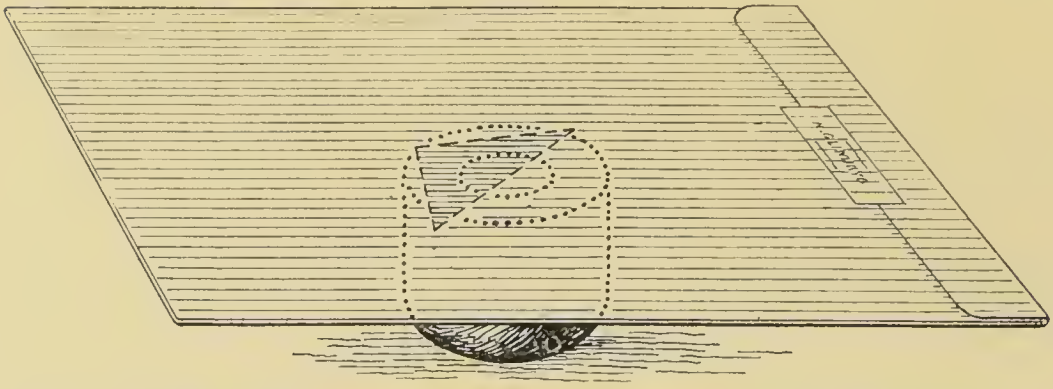


Fig. 2.—Diagram of the Method of demonstrating Secondary Radiations.

have produced a much greater effect, while the aluminium has absorbed about half of these radiations (Fig. 3).

Physical Considerations affecting Treatment

The rays are given out in all directions, they are neither reflected nor refracted to any appreciable extent, and so, apart from secondary radiations given off from the radium apparatus, the only substances which influence their action are those between the radium and the patient. Recent work has

demonstrated the refraction of X-rays by crystals and their reflection by mica, so that our views about radium rays may need to be altered in the future. The maximum effect, then, will be obtained by having the radium surrounded by the tissues on which it is desired that its rays should act, and for this it is

FIG. 3.—The Action of the Secondary Radiations on a Photographic Plate.

necessary that it should be placed in a tube. On the other hand, for acting evenly on a surface it is preferable that the radium should be evenly spread on a flat applicator and the radiation from one side of it only is used.

If the source of radiation is a point, the intensity of the rays varies inversely as the square of the distance. This law is almost true for the small tubes that are

in practical use; in these the radium salt should be compressed into the smallest possible space and is almost a point. The amount of radiation is entirely dependent on the amount of metallic radium present and the thickness of the substances the rays have to traverse. It is obvious that in very impure specimens the impurity will itself act in some degree as a filter: this hardly affects the γ-rays, but even if these alone are used, there is the very serious disadvantage that an impure salt takes up more room and is not able to be contained in so compact an apparatus.

It is possible, though it is not economical, so to use the radium that the rays from an enormous quantity can be made to radiate from a point the size of a pin's head: if, for instance, the emanation from a gram of radium is drawn off by a vacuum pump from a solution of the chloride,[1] dried, and then condensed in a small vessel, immersed in liquid air, this will in a few hours give off a radiation almost as active as that from the original radium; its strength, however, will gradually diminish, falling to half value in 3·85 days.

In a flat applicator, on the other hand, it may be an advantage to have the salt somewhat impure, as this makes it more bulky and it can then be more easily spread over a large area.

When a sheet of metal or other substance is used to cut off a portion of the radiations, this is usually known as a filter or screen.

[1] The emanations may also be obtained by heating the salt to redness.

CHAPTER II

INTERNAL ADMINISTRATION OF RADIUM

This falls into two distinct methods :—

1. The internal administration of radium itself.
2. The internal administration of the emanation.

As will be understood from Chapter I., practically all the properties of radium which are medically useful can be obtained from the emanation, with, however, the very great difference that the action is evanescent because the emanation decays much more rapidly than a radium salt.

Internal Administration of Radium Salts

(*a*) *By the Mouth*

The toxicity of radium salts administered in this way is not known, as it is far too expensive a substance with which to perform these experiments. There is no doubt that, if a sufficiently large quantity were used, it would be intensely irritant, and the actual contact with the mucous membrane of the stomach for the length of time it remained in that organ would cause severe burns to develop. Bellingham-Smith[1] has worked out the distribution and excretion of radium in the organs of mice. Even when injected subcutaneously, the majority is excreted by the small and large

[1] Bellingham-Smith, *Quart. Journ. Med.*, vol. v., No. 18, p. 249.

intestines and about 10 per cent. by the kidneys. In the distribution in the system, the notable fact is the comparatively high radio-activity of the kidneys and lungs. The accumulation in the latter is suggested to be due to an attempt by the organism to get rid of the emanation which is excreted largely by the lungs. The radio-activity of the tissues diminishes rapidly but does not entirely disappear for several days. There is no evidence in mice that the liver or the skin plays any part in the excretion.

In practice, radium salts are not given internally as they can be so efficiently replaced by the emanation, and that without any loss of the parent substance, whereas if the radium salt were given by the mouth it would either be impossible to recover it or the difficulties of doing so would make the administration an extraordinarily costly one. An exception must be made in regard to the waters of Kreuznach, which contain minute quantities of radium salts. We may leave the discussion of this method of treatment with the remark that, in the administration of radium by the mouth, all the effects of the emanation must be obtained, in addition to any effects the radium itself may have, owing to the fact that the emanation is continually given off from the radium : the action is therefore spread over a long period while the radium salt is being slowly excreted.

(*b*) *By Injection*

Owing to the excretion of radium salts by the intestine,[1] the hypodermic or intra-muscular injection

[1] Bellingham-Smith, *loc. cit.*

of a soluble salt would have some advantages over administration by the mouth, as the solution would have to be carried into the blood before it was eliminated. The injection of an insoluble salt of radium seems to have many possibilities: though it retains a good deal of the emanation in itself, it will continually be setting free a proportion of its total amount of emanation which is carried into the body. The radium salt itself will constantly be exerting the action of its rays and those of the active deposit (from the emanation entangled in it) on the part with which it is in contact, and it is found that, as these insoluble salts are absorbed extremely slowly, the action will proceed over a considerable period. This method has been used in the treatment of rheumatoid arthritis [1] by injection into the affected joint, and it has also been used for injection into the substance of growths, but this latter method has not given very successful results.

(*c*) *By Ionisation*

This is a very complex subject, for it must be remembered, in the first place, that the introduction of a substance in the ionic state will not have the same effect as the introduction of that substance in the form of a salt. Haret [2] has shown that radium ions can be driven deeply into the tissues, and that they are not deposited in the corium as might be

[1] Chebrier, "Treatment of Rheumatism with Insoluble Salts of Radium," *Gaz. d. hôp.*, Paris, May 17 and 19, 1910, tome lxxxiii., No. 56, p. 807; *Presse méd. belge*, Bruxelles, July 16, 1910, No. 57, p. 552; *Arch. d'Électricité Médicale*, June 10, 1911.

[2] Haret, *Compt. rend. Acad. de Sc.*, Paris, 1911, tome clii., pp. 800–802; also Béclère, *Acad. de Méd.*, Paris, 1911 (3), tome lxv., pp. 563–576.

expected from an analogy with calcium salts.[1] It is a costly method, as the radium introduced is practically lost, and probably this accounts for the very small amounts which have been used in the experiments. Haret claims good results in the treatment of malignant growths by this method, but he used extremely small quantities of radium—small fractions of a milligram; and it is quite possible that, had he used larger quantities, his results might have been even more successful. He claims that the radium is carried into the tissues to a depth of even 9 or 10 cms., but if the amount of radium was estimated by the radio-activity, the possibility of the radium itself only going into the skin and the emanation and active deposit being carried into the deeper tissues has always to be considered: whether the active deposit can be ionised and introduced in this way is not known, as its chemical properties are not thoroughly determined. Radium C probably can, as it is possible to deposit it electrolytically from its salts, and the same is also probable in the case of radium D, E and F, but one may safely assert that it is impossible to drive in the emanation itself, for it is chemically an inert gas forming no combinations, and therefore the solution of it will contain no ions.

Internal Administration of Radium Emanation

(*a*) *By the Mouth*

This method is now being very largely used, especially in Germany, but generally with extremely

[1] Finzi, "Some Experiments with Ionic Medication," *Brit. Med. Journ.*, London, Nov. 2, 1912.

minute quantities : one frequently hears of quantities as small as 1000 Mache units or less. One Mache unit = $4{\cdot}5 \times 10^{-10}$ Curies, and a Curie is the amount of emanation in equilibrium with 1 gram of radium : from this it can be deduced that 1000 Mache units are approximately the amount of emanation in equilibrium with $\frac{1}{2000}$ mgrm. of radium. Now the emanation from 200 mgrms. of radium has been used in the treatment of disease, and though when this emanation is drawn off daily it corresponds only to that obtained from about 25 to 30 mgrms. of radium in equilibrium, it will be seen that its activity will be about 40,000 times as great as that mentioned above. But the extraordinary fact is that these very small quantities, nevertheless, exert an effect upon the human body. It may be mentioned here that the waters of Gastein, the strongest natural radio-active spring, contain less than 250 Mache units per litre.

It will not be overlooked that in this treatment there will be substances circulating in the blood which will give off a large amount of α-rays, an amount, in fact, which will be ten times as great as that of the β-rays : it is probable that these α-rays have an effect different from the other rays of radium, and differences have been shown by certain experiments in which the total rays were used, firstly alone, and then with the α-particles screened off. In external methods of treatment by radium these α-particles never get through the outer epidermis, and consequently do not exert any influence, but when the substances generating them are being carried about in the blood stream there will be no impediment to their exerting their

full power. The emanation is soon excreted, chiefly by the lungs, so that, if taken internally, it is removed a very short time after it has entered the blood stream. Thus, if a solution is swallowed with a meal, it is not entirely absorbed from the stomach for nearly four hours and it is completely eliminated in about four hours. After the emanation has disappeared, however, there will still be the active deposit (Ra A, B, etc.) in the body that has formed as a result of the decay of the emanation, and how long this persists or how it is excreted is not yet determined, as so few experiments have been made with a large enough amount. Although the emanation only decays to half value in four days, yet all trace of it has disappeared from the body in a few hours, showing the rapidity of its elimination.

The methods of preparing the solution are as follows :

1. The best way is to have a radium salt in solution, and, by means of a mercury pump, to withdraw the emanation every day. As the radium will have decomposed some of the water in which it is dissolved, the emanation will be mixed with a quantity of oxygen and hydrogen gas, but this can easily be removed by having two platinum wires sealed into the vessel in which the emanation is collected and passing an electric spark between them, which at once explodes the oxygen and hydrogen so that only the emanation is left : [1] this is then dissolved in water and kept in a bottle with a tightly fitting stopper for use during the day. The emanation being a gas with a high density is much more soluble than lighter gases, such as the gases of the atmosphere, and so can be dissolved in a

[1] A slight excess of hydrogen occurs from some unexplained cause.

comparatively small quantity of water. The bottle containing the emanation solution should be full and be kept inverted in order that there may be no danger of air leaking into it and gradually displacing the emanation from the solution. It has been shown that when administered by the mouth the emanation is excreted in four hours; it will therefore be advisable to administer the solution of the emanation in frequent small doses, but it must be borne in mind that it will not keep, as it falls to half strength in 3·8 days.

Fig. 4.—Emanation Apparatus, method 2.

2. The radium in the form of an insoluble salt mixed with some other insoluble substance is contained in a porous earthenware pot, and this is placed in a glass vessel containing a comparatively large quantity of water. Into the stopper of this is fitted a second vessel so that a certain definite quantity of water is drawn off every day and replaced by filling the upper reservoir; by this means the amount of water in contact with the radium is kept constant (Fig. 4). This method is a wasteful one, for, as has been pointed out, insoluble salts of radium retain a large quantity of emanation within the granules of the salt. It is,

however, an extremely simple and convenient method, and one which any one can manipulate. An even better way would be to filter the water through a quantity of powdered pitchblende concentrate. It seems probable that by this method the radium is gradually but very slowly dissolved in the water. If the carbonate is used, care should be taken to use only recently boiled water, so as to avoid any carbon dioxide which might form a soluble bicarbonate analogous to that of calcium.

Fig. 5.—Emanation Apparatus, method 3.

3. A similar method of preparing the radio-active water is to have an insoluble radium salt in a small cup which is arranged in an apparatus as in the diagram (Fig. 5). The radium packed in by cotton wool is contained in the cup C and is sealed off from the hollow tube E, which is connected with an upper vessel B; this glass tube has orifices just beneath the cup from which the water, which is poured into the upper vessel B, escapes into the lower vessel A. D is an air seal, so that as the apparatus is emptied only a small quantity of air

can come in contact with the surface of the water, otherwise some of the emanation would escape. A is first filled with water and then the inner tube inserted and B filled; the amount of water in B measures the daily dose, and it is filled every day. Naturally, it takes some days after the installation of the apparatus for the emanation in the water to reach equilibrium, but when it has attained its maximum it remains constant.

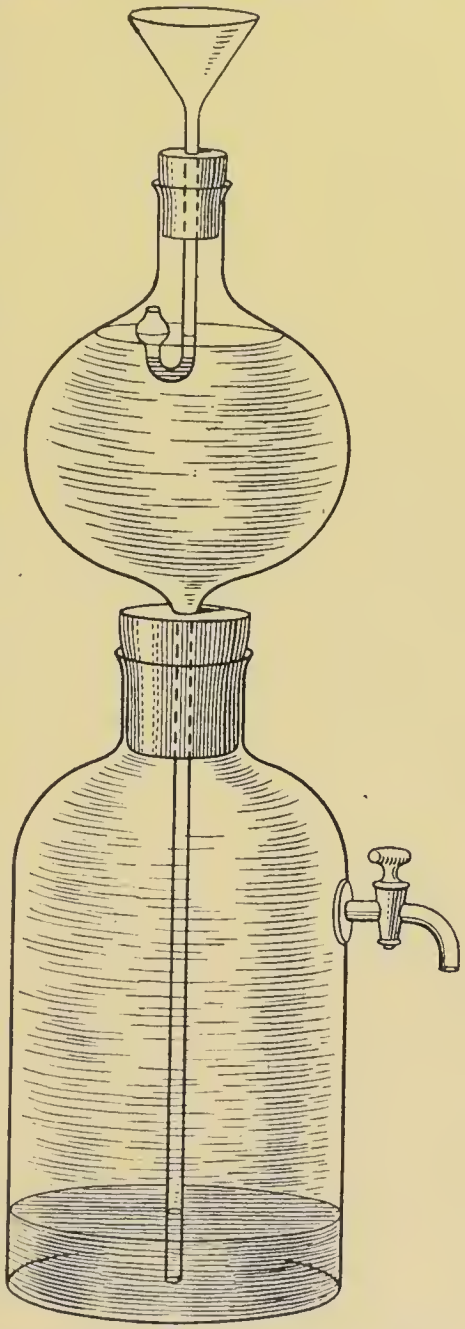


Fig. 6.—Oil Emanation Apparatus.

4. A method, which has been suggested to me by Mr. C. E. S. Phillips, is to have a vessel like the above, but with the tap at the top. At the bottom of the bottle is placed a solution of radium chloride in water and this is covered by some oil such as liquid paraffin. The emanation is much more soluble in the oil than in water, and would pass into it, when it could be drawn off by the tap. A definite quantity of oil is added and a definite quantity drawn off every day.

A suggested apparatus for this is shown in Fig. 6.

It is apparently immaterial whether the emanation is administered by the mouth or by the lungs, therefore its action and uses will be discussed subsequently.

(*b*) *By Inhalation*

It is found that, when the emanation is inhaled, it is excreted much more rapidly than when taken by the mouth, thus allowing less of the active deposit to be formed in the system. In all probability the rate of excretion really depends on the amount of emanation that gets into the blood, for the excretion is chiefly by the lungs, in whatever way it is administered. It will be interesting in connection with this method of treatment to recall that it is stated that the miners working in uranium mines never suffer from rheumatism or gout, and this was probably one of the reasons for the adoption of the emanation method of treating these diseases. It is obvious that the ideal way of employing this inhalation treatment would be a continuous inhalation of small but definite quantities of the gas; the quantity in the blood would soon establish a constant relation to that in the air, the amount excreted being balanced by the intake; there would then be a continuously increasing amount of active deposit in the system which would take a very considerable time to reach its maximum. For convenience, however, it is found necessary to use larger quantities and administer them over a much shorter time. The inhalation may be made in several ways, and is sometimes combined with inhalation of oxygen. In one method a small room[1] is filled with the emanation mixed with oxygen and

[1] Known as an "inhalatorium."

in this room the patient sits, the breathed air is purified by being continually passed over caustic soda and returned into the room, so that the emanation is not lost, the supply being kept up by a stream of oxygen gas passing through tubes lined with a layer of radium salt. The objection to this method is that, although the carbon dioxide can be removed from breathed air by caustic soda, there are other products of respiration which are far more poisonous, and it is, to say the least, doubtful whether the powerful oxidising properties of the emanation would in the quantities used be sufficient completely to destroy these noxious substances. What seems a more rational method is to inhale a stream of air or oxygen, which is carried over salts of radium in the same way as in the other method, and to exhale this again into the open air through a valve : it must be admitted, however, that this is somewhat wasteful. The results of the treatment do not differ appreciably from the administration of the emanation by the mouth, but, when oxygen is given as well, the stimulating effect of this must be taken into account. The use of emanation baths is also largely an inhalation method, only a very small amount of emanation being absorbed by the skin. It has been proved that, if the patient be prevented from inhaling the air over the bath by being supplied with air from another source, the amount of emanation absorbed is much reduced. The radio-active bath, except as a method of hydrotherapy, seems to present serious disadvantages over the inhalation or internal administration, as the amount of emanation in the air above the bath is not definitely known and the dose cannot therefore be accurately gauged.

The administration of emanation intravenously and hypodermically has not, to our knowledge, been used in practice.

External Applications, Baths, Poultices, etc.

It has just been stated that a small quantity of emanation is absorbed through the skin, and this is taken advantage of by the use of poultices containing small quantities of radium in the form of what is called "radio-active mud." They have been used with some success in France, and one's own experience shows that they have some slight value. The poultice, however, should contain much more radium than that usually supplied in the radio-active earths.

Action of the Emanation

The emanation acts by increasing the rapidity of tissue oxidisation and by increasing the activity of all the body ferments. Whether *in vitro* or *in vivo*, experiments have shown that, in the case of every ferment it was possible to test, the presence of radium emanation in small quantities increased the rapidity of its action. Consequently metabolic interchange is more rapid and elimination of waste-products more complete.

Medical men and others employing the emanation in therapeutics have unfortunately been less careful than those employing the rays of radium not to overstate their case, and as a result cures have been claimed for a variety of diseases such as would ordinarily grace the advertisements of a patent medicine. To add to the difficulties of earnest workers in this branch of

therapy, numberless so-called radium preparations have been produced which contain the minutest amounts of emanation.

Little exact work has been done on the action of the emanation, though clinical observations, especially at various spas, are numerous. It has been shown to have a powerful bactericidal effect which seems to be due chiefly to the emanation itself, as a very thin sheet of mica considerably diminishes it:[1] the power of opsonins is reduced by the emanation but the action is less marked, and, though the phagocytic power of leucocytes is gradually diminished and the leucocytes are eventually themselves destroyed, this action is still less pronounced.[2]

It is claimed by Gudzent[3] that the emanation renders uric acid and urates more soluble, and he and other writers have shown that it increased the activity of the various body ferments. It certainly acts as a tonic, and it seems probable that in sufficiently large doses it would be poisonous. Owing to the accumulation of the active deposit in the body, especially of radium D, E, and F, it is possible that the effect is cumulative, but this would only be appreciable if large doses were given.

That small doses have some effect is shown by the results of treatment at some spas. It has long been known that certain springs were of use only when swallowed at their point of emergence, and, when bottled and sent away, had no action. Apart from the

[1] Chambers and Russ, *Proc. Roy. Soc. Med.*, Pathol. Section, May 1912.

[2] Chambers and Russ, *loc. cit.*

[3] Gudzent, *Deutsches med. Wchnschr.*, Leipzig, 1909, Bd. xxi.

benefits of regulated spa treatment these springs appeared to exert a medicinal effect, though they usually contained a very small amount of salts. They have now been shown to have radio-active properties. Greater effects are, however, obtained by using larger amounts of emanation and the amount of that gas that can be obtained from $\frac{1}{2}$ to 5 mgrms. of radium bromide may be used daily without harm—in fact, much larger quantities have been employed. However, 1 or 2 mgrms. will often give satisfactory results.

There is no doubt that some extraordinarily good results have been obtained by this method of treatment in cases of chronic gout, and this seems to be its chief use. After taking the radio-active water (or inhaling the radio-active gas) for a few days there is a reaction, and the affected joints become red, swollen, and painful, but the administration should not be discontinued at this time, as the reaction passes away in a day or two and is followed by a diminution of pain and stiffness and a slow but gradual improvement. Bone deformities, of course, remain, but the softening of adhesions, etc., greatly improves movement when it was formerly restricted. Acute gout will be better treated by ionisation with lithium and iodine ions.

Beneficial results have also been obtained in certain cases of rheumatoid arthritis, and benefit has been claimed in many varieties of chronic inflammation, even myocarditis.

The emanation has been shown to be excreted by the kidneys[1] to a certain extent, and this may partially account for its beneficial action in Bright's disease: but it has also been shown that the blood-vessels of the

[1] Bellingham-Smith, *loc. cit.*

periphery dilate under its influence without any weakening of the heart's action, while the blood pressure of course falls, and this, again, may have something to do with the benefit derived in this disease. Another action of the emanation is to increase the amount of hæmoglobin and the number of erythrocytes while the leucocytes are diminished. It has, therefore, also proved useful in chlorosis and other forms of anæmia, but no marked results have so far been reported in leukæmia.

Good results are also said to have been obtained in diabetes.

In cancer it has been said that it increases the activity of the autolytic ferment and so causes retrogression, but it seems possible that it might also increase the ferment which assists the advance of the disease, and so these results must be accepted with all caution.

Some of its action in these diseases is possibly due to its bactericidal effect.

CHAPTER III

HISTOLOGICAL, PHYSIOLOGICAL AND PATHOLOGICAL ACTION OF RADIUM RADIATIONS

In discussing the action of the three types of radiation, it has unfortunately been too generally assumed that they will all have the same effect in proportion to the amount which is absorbed ; that the α-particles, being completely absorbed, will have far the greatest effect, but that their action will be of the same nature as that of the β and γ. While it is difficult actually to disprove these assertions, clinical results most strongly favour the view that they are not true. It does not follow that because a particle is stopped in a tissue that it is going to have one particular effect on it whatever the nature of that particle ; it may, but it is quite easy to understand that particles of a different nature might have a totally different effect. We do not expect the same result to occur if a man is hit by a cricket ball as would, if he were struck by a bullet : it is true that either *might* kill him, but we know that the latter is much more likely to have a serious effect. It also does not necessarily follow that because a particle or ether wave is stopped in a cell that it will have more effect than if it passed through that cell, as it is quite possible to imagine the actual passage of the particle through the cell producing a pronounced change in it. If a man is struck by a rifle bullet which passes right

through him, it would be absurd to say that that bullet will not injure him because it is not stopped in him, and yet it is frequently said that if a ray or particle passes through a cell and is not stopped it will produce no change in that cell. It is granted that it is probable that a stopped particle may be more likely to produce the death of the cell than the particle which passes through. To pursue the analogy, the soft-nosed bullet which is stopped in the body is more likely to kill than the modern hard bullet which passes through. But it is very seldom tissue death that we aim at in radium treatment; this can be excellently produced by the actual cautery, or, if a deeper action is required, by the diathermic method; it is tissue change that we require as a rule, and not tissue death. The latter is sometimes produced in obtaining the former; for instance, when the radium is inserted into a malignant tumour, tissue death is produced in the central portions of the tumour by over-dosing them in order that the peripheral portions shall receive a sufficient dose to produce the changes required. Further, with regard to the nature of the radiations, it is known that the α- and β-radiations are of a very different nature, in that the former have very much larger particles than the latter; there is considerable doubt as to the nature of the γ-radiations, but most people believe them to be ether vibrations and not particles, and though their action may be the same as that of particles there is no essential reason for assuming, without proof, that it is.

α-Rays

We have, unfortunately, to record that we know of no experiments with pure α-rays which have yet

been performed: they could be, by using polonium, which is radium F, the final radio-active product of the series of substances in the active deposit of radium; this gives off α-rays only, so that it is possible to use these without the β- and γ-rays. In using the emanation for treatment we may consider that we are using chiefly α-rays, as they preponderate over the β- and γ-rays; nevertheless, the β- and γ-rays may have an effect out of proportion to their amount. In some cases experiments, done first with all the rays and then with the β- and γ-rays only, have shown that certain effects are due to α-rays only. One result shown in this way is the disappearance of Altmann's granules in healthy tissue submitted to the action of all the rays, which does not occur when the β- and γ-rays only are used.

β-Rays

The action of the β-rays cannot be separated completely from that of the γ-rays, but, when the α-rays are filtered off by $\frac{1}{20}$th mm. of aluminium or its equivalent, the action of the mixture of β and γ is different from that of the γ-rays alone. There is a method of still further increasing the proportion of the β-rays to the γ-rays, and one which could with difficulty be used experimentally to determine the difference in action, and this is deflection of the β-rays by means of a strong magnet. In this way, the β-rays can be concentrated in a small area, leaving some of the γ-rays still acting on this area but acting equally on a much larger area round about (see p. 8). There are great practical difficulties in such an experiment, but they can no

doubt be overcome; it has not, however, to our know ledge hitherto been performed.

Histological Action of the β-Rays on Normal Tissues.

There is an excellent description of the action of radium rays and experimental work on this subject in a little book by London.[1] Though the experiments on the action of radium rays are not described as being due to the action of the β-rays, the use of the radium in thin glass tubes without any metallic filter ensures that a very large proportion of the β-type are used, the glass tube cutting off the α-particles. In some of the experimental work done in this line the great mistake has been made of observing the results too soon after an application: the changes during the first few days are of great importance, but those which occur after two or three weeks are equally important. Any experiments on the action of radium rays on the tissues should include observations of the changes for varying times after the irradiation has ceased, owing to the great latent period in the action of some of the rays. Most of the experiments also have been performed with toxic doses, while there are very few records of experiments with therapeutic doses. The experiments of Dominici and Barcat [2] on the action of radium rays on the skin and subjacent connective tissue are free from these criticisms as they are far more complete and far-reaching.

There is a consensus of opinion that the β-rays act

[1] *Das Radium in der Biologie und Medizin*, Leipzig, 1911.

[2] Dominici and Barcat, *Arch. gén. de méd.*, Paris, July 1909.

differently on different organs and different tissues. One of the tissues the most sensitive to the radium rays is the endothelium of the blood-vessels, and as this forms a constituent in varying degree of every different tissue and organ it will, apart from the constitution of the tissue itself, have a very great influence in the results. For instance, Finzi and Horsley,[1] in some work with mixed β- and γ-rays on the brain, came to the conclusion that the changes were due almost entirely to changes in the blood-vessels, while the direct action even of large doses on the cerebral tissues seemed to be extremely slight. Thus it will be found that the more vascular tissues are more injured by the rays than less vascular ones. It is of interest to note here the experiments of Halkin,[2] who found that after the action of the rays on the skin, before there were any epithelial changes there was a perivascular injection, then dilatation and engorgement of the small vessels, a swelling, and, later, a vacuolation of the endothelial cells; still later there was a vacuolation of the muscular sheath and a strongly marked dilatation of the capillaries of the adventitia. Goldberg also noticed the same alterations. These changes explain why the effects of radium persist so long, as not only is there damage to the tissues but their blood supply is disturbed by the damage to the vessels. It is found that gland cells are very susceptible to the action of the rays, especially the cells of the ovary and testicle. London and Horowitz place the sensi-

[1] "A Note on the Action of Filtered Radium Rays applied directly to the Brain," *Brit. Med. Journ.*, London, 1911, vol. ii.

[2] "Ueber die Einfluss der Becquerel strahlen auf die Haut," *Arch. f. Dermat. u. Syph.*, Wien, Bd. lxv. S. 201.

bility of the various tissues in the following order, reckoning by the thickness of the tissue affected by the insertion of a radium tube into it for a definite time: firstly, nerve tissue, then lymphoid tissue, the genital glands, the liver and the omentum, which react with nearly the same intensity to the radium rays; the kidneys, supra-renals, muscle, cartilage, and blood-vessels follow them; and, lastly, come the salivary glands, the pancreas, and mucous membrane. These results are in some cases, *e.g.* nerve tissue and blood-vessels, at variance with our own. Goldberg also finds that the mucous membrane has one-twentieth the sensitiveness of the skin. So far as clinical experience goes it can be affirmed very definitely that the mucous membrane, except in the vagina, is *more* sensitive than the skin, and a smaller dose will produce a visible macroscopic reaction in mucous membrane than in skin.

No organ is unaffected by radium rays provided the intensity be sufficiently great and the exposure sufficiently long.—This does not mean that the intensity must be large, but there must come a point at which in order to produce any effect with a weak preparation of radium it has to be left on continuously, while with a still weaker preparation it will be impossible to leave it on long enough to produce any effect.

Every tissue reacts to radium in its own specific way.—Thus, the endothelium of blood-vessels swells up enormously, and subsequently, if the dose has been sufficient, degenerates and disappears: in a glandular structure, on the other hand, the cells are not observed to swell up, but they lose their staining power and disappear or are removed by leucocytes. In many tissues the

action produced is, in part, due to the destruction of the blood-vessels, as has been mentioned above in the case of the brain.

The dose required to destroy different types of cell varies very greatly.—For instance, gland cells may be destroyed by a dose which does not harm the cells of connective tissue or the skin. In other words, the sensitiveness to the action of the radium rays varies with the type of the cell, and this is what is meant by the *selective action* of radium rays. This important fact will subsequently be shown to apply also in certain diseased conditions.

In general, radium rays in small doses have a stimulating and in large doses a destructive action.—From what has been stated above, however, it will be seen that the same dose that will stimulate some cells will destroy others which are more sensitive to the rays.

There is always a latent period after the application of the rays before the occurrence of changes in the tissues.—Naturally, exception must be made to cases where the actual application is so prolonged that it covers the latent period caused by its own initial stages. The larger the dose the shorter will the latent period be. Microscopical changes will occur before any that are visible to the naked eye, and while the latent period observed for a moderate dose may be two or three weeks, histological changes in the tissues may be seen within a few days. From the difference between results with filtered and unfiltered rays it seems that the latter have a shorter latent period than the former.

The actual cause of the changes that result is not known, and several theories exist. According to Horowitz, there seems to be a definite relationship

between the sensitiveness of a tissue and its chemical composition. Attempts have been made to show that the action is due to the formation of decomposition products of lecithin, more particularly of choline, but though this may partly account for the changes observed it does not entirely do so. Another theory ascribes to the rays the power of destroying young cells or of inhibiting the reproductive power of cells so that no effect appears until the older cells die off in sufficient numbers and there are no younger ones to replace them : this theory also has many deficiencies.

The changes which occur in the skin and subcutaneous tissues are extremely well described by Dominici and Barcat,[1] who, using guinea-pigs, gave doses sufficient to cause an erythema ten days after the exposure, followed by an ulceration about three weeks after, which got covered by a crust that fell off between the fifth and sixth week, leaving a white cicatrix where the skin was unpigmented, epilated, smooth, and supple. The amount used was 6 mgrms. of pure radium bromide spread over a circular surface 2 cms. in diameter, and the length of exposure was fifty minutes (ten days 5 minutes each). Irritative lesions appeared in the epidermis eight or ten days after the commencement of the application characterised by intercellular œdema and hypertrophy of the epidermal cells, the nucleus of which enlarged and became irregular. The epidermis separated between the fifteenth and twentieth day. During this period the hair follicles, the sebaceous glands and the sweat glands underwent a granular and pigmentary degeneration which ended in their destruction. The

[1] *Loc. cit.*

dermis was at the same time the seat of an intense congestion and of the beginning of an embryonic transformation, which became more marked in the period immediately following cicatrisation. Thirty or forty days after the experiment, the restoration of the epidermis was complete, while the hairs, sebaceous and sweat glands were permanently destroyed. The connective tissue of the skin was transformed into embryonic connective tissue, the fibrous and elastic tissue having almost completely disappeared and become replaced with numerous fusiform connective tissue cells with ramifying and anastomosing processes. The smooth muscle fibres underwent a similar transformation and could not be distinguished from the other embryonic tissue cells. The tunics of the arterioles and venules were similarly changed so that they looked like enormous blood capillaries. The endothelium acquired the plasmodial structure of the embryonic state, and the capillaries at the same time dilated and grew actively. In the next phase the size of the blood cavities had diminished and the capillaries retracted until their lumen almost or quite disappeared. The embryonic cells lost their embryonic character and began to form fibrous tissue. This new fibrous tissue, however, is different from the original connective tissue, as it is arranged with all the fibres parallel to the surface instead of the interlocking fibres seen in the normal connective tissue. It differs also from post-inflammatory cicatricial tissue by its regularity, uniformity, the absence of perivascular fibrous bands, and vascular obliteration. Six or seven months after the experiment the cells became thinner and their nuclei flatter, while their chromoplasm disappeared

to merge into the hyaloplasm; connective-tissue cells separated the layers of fibroblasts, while the elastic tissue was reformed in increasing quantity. Nevertheless the regular arrangement of cells parallel to the skin still persisted. Larger applications led to the production of superficial or deep scars followed by permanent changes. After applications of ten to fourteen hours the scar reaches the dermis, and the process of repair is not effected until three or four months, and is followed by irregular cicatrices. Applications with the same apparatus coated with lead $\frac{1}{2}$ mm. thick and with paper or indiarubber outside this leads to similar changes, but very much longer applications are needed.

On the cells of the brain moderate doses cause changes in localised areas which appear to be due to thrombosis of small vessels—only with very large doses are the nerve cells themselves damaged—and there occurs an absorption of chromatin substance and destruction of nuclei in the neuro-fibrillary network. Nerve fibres become thickened under these conditions, and the peripheral nerves show changes in the axis cylinder and destruction of the myelin sheath.

Glandular tissue is usually readily destroyed, as was shown by Dominici's experiments on the skin, and this also applies in the case of other glandular structures, the cells of the testicle and the ovary being especially sensitive. Necrosis of the epithelium of the seminal canals and destruction of the spermatozoa characterises the action on the former, and atrophy of the Graafian follicles that on the latter. The salivary glands and the pancreas are said by London only to react weakly.

The lymphatic organs are very sensitive to the rays, the action being characterised by a destruction of the lymphoid cells. This behaviour is shown also in the spleen and bone-marrow, but in the latter with the destruction of the leucocytic cells there occurs an increase of the erythrocytic series.

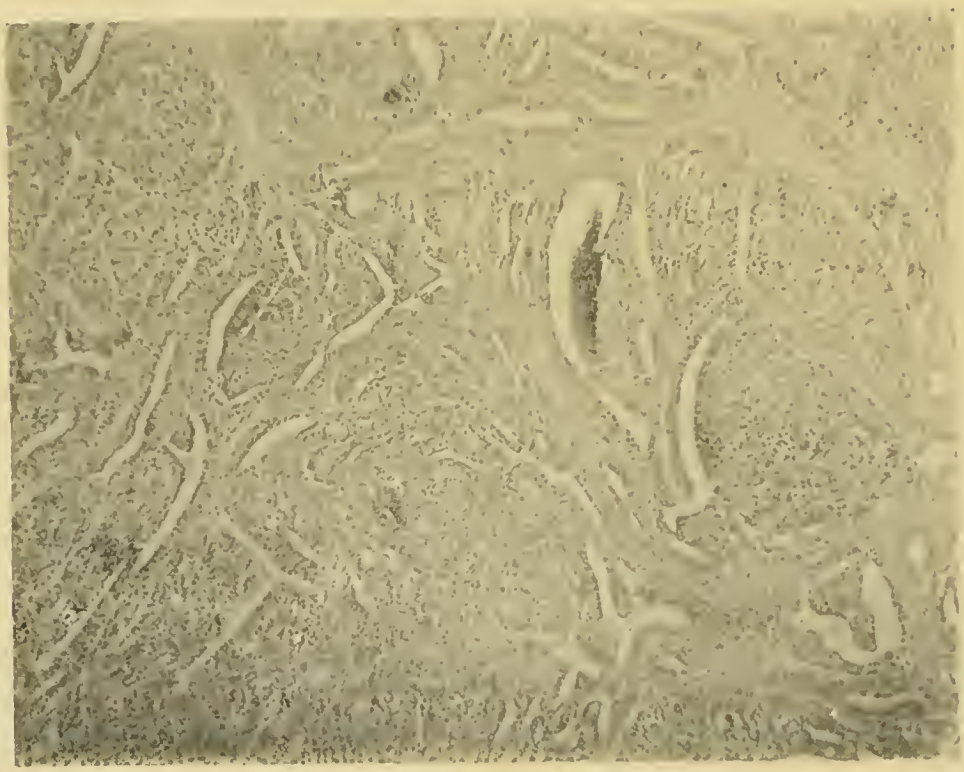


Fig. 7.—Tumour of Palate (untreated).

Muscle tissue degenerates under the action of the rays. Cartilage is very little influenced and even with large doses shows increased growth.

Endothelium of blood-vessels is extremely sensitive to the rays, and with small doses swells up enormously and may completely obliterate the lumen of the vessel, while larger doses cause its destruction.

Histological Action of β-Rays on Diseased Tissue

The action of β-rays on malignant growths varies considerably with the type of cell comprising the tumour. In any tumour it is possible to get necrosis if

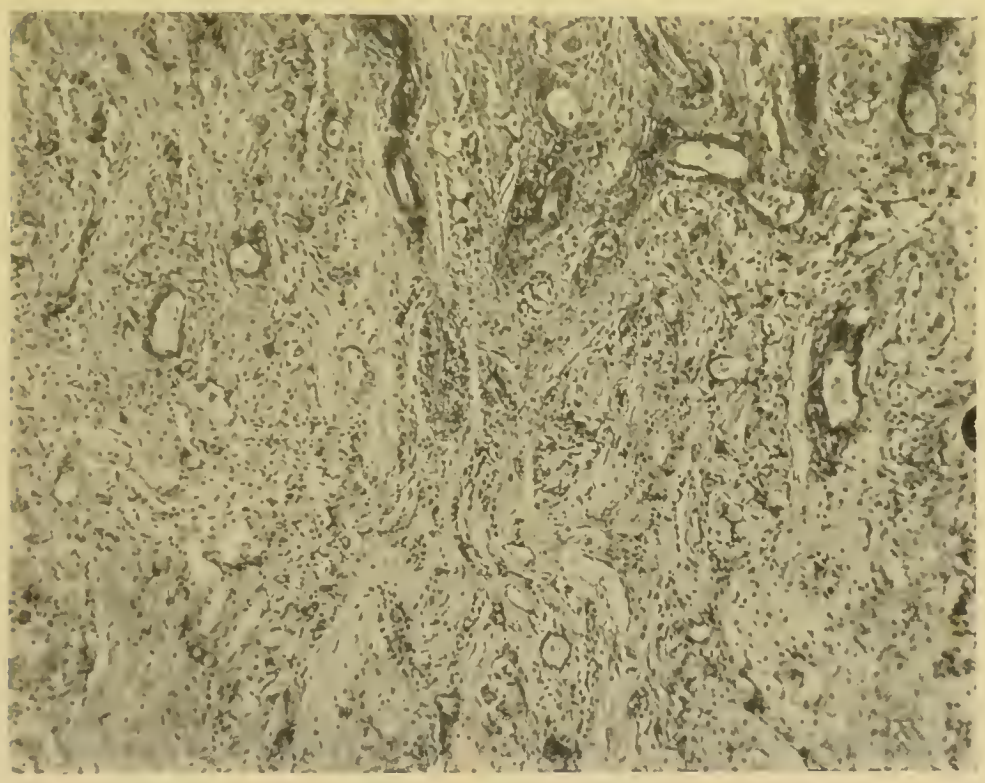


Fig. 8.—Tumour of Palate (recurrence), two weeks after treatment.

a sufficient dose of the rays is given, but if the less penetrating β-rays are filtered out, much greater doses can be given without necrosis than healthy tissues would stand; γ-rays are being given at the same time, but when the filter used is $\frac{1}{2}$ mm. of platinum or less, their action is probably overpowered by that of the β-rays. In a tumour which does not respond readily to the action of the rays there is more necrosis and less

absorption than in one which reacts well. Fig. 7 shows a microscopical section of a tumour which started in the palate. This was removed surgically at a time when the whole upper jaw was involved. A recurrence took place in the orbit, and Fig. 8 shows the result of treating this with radium, the specimen being removed

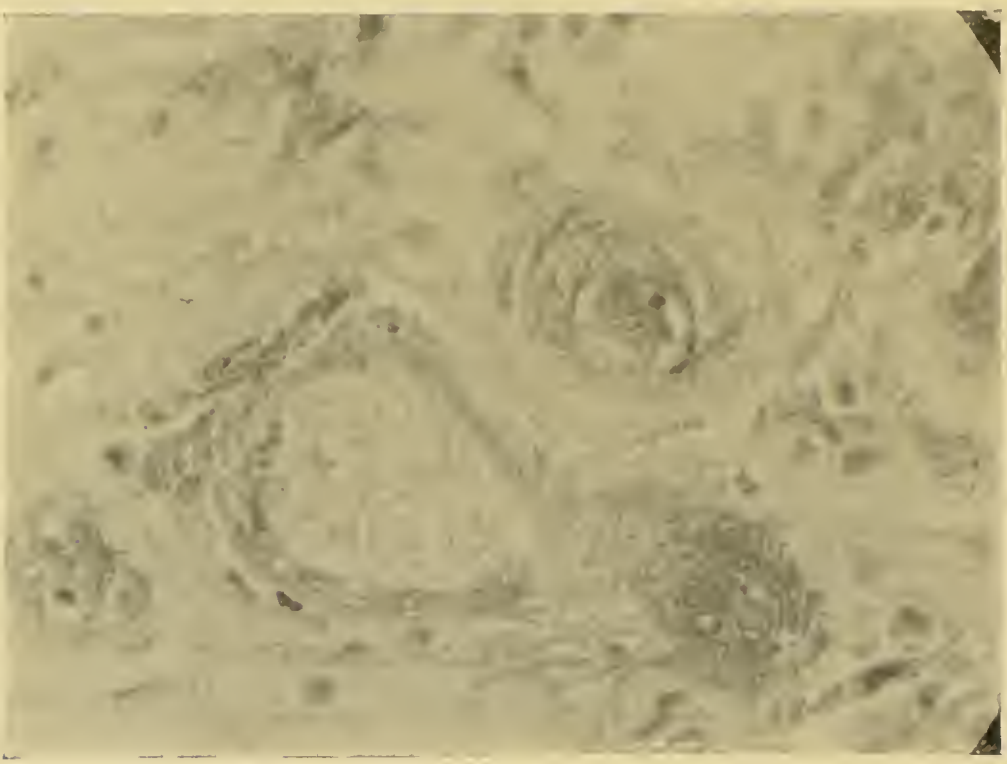


Fig. 9.—A portion of Fig. 8 more highly magnified.

a fortnight after treatment. The filter used was supposed to be $\frac{1}{2}$ mm. of silver, but proved to be inaccurately manufactured and was rather less. A most notable feature in the second section is the enormous proliferation in the endothelium of the blood-vessels, some of which are shown enlarged in Fig. 9, and it is possible that this may have much to do with the effects of the radium.

An increase of fibrous tissue is always seen in a growth some weeks after the application. In some cases it is possible that the connective tissue, which was present between the groups of cells of the growth, may, after their destruction, form a much more prominent object in the microscopic field owing to the disappearance of enormous cellular masses, but it is more probable that a considerable part of the fibrous tissue is a new formation and due probably to an inflammatory reaction set up in the growth. It is preceded by a leucocytic infiltration indicating that an inflammatory change takes place. The cells of the growth become absorbed, and in a successful case nothing but the fibrous tissue remains. The difficulty in a human being of obtaining sections from a growth at frequent intervals after an application militates against a successful and complete observation of the series of changes, which occur both with these rays and the γ-rays; there is also the possible danger that cutting through the growing edge at a time when the tumour is not fully under the influence of radium, might facilitate extension of the growth to deeper parts.

Histological Action of γ-Rays

The changes that seem to occur in a growth which responds to radium rays, filtered through 2 mm. of platinum and therefore consisting chiefly of γ-rays, seem to be—firstly, a loss in the staining power of the cell nuclei of the growth, and then an actual disappearance of the cell itself; there is a certain amount of leucocytic invasion of the growth, but this does not appear so marked as after β-ray treatment, and less

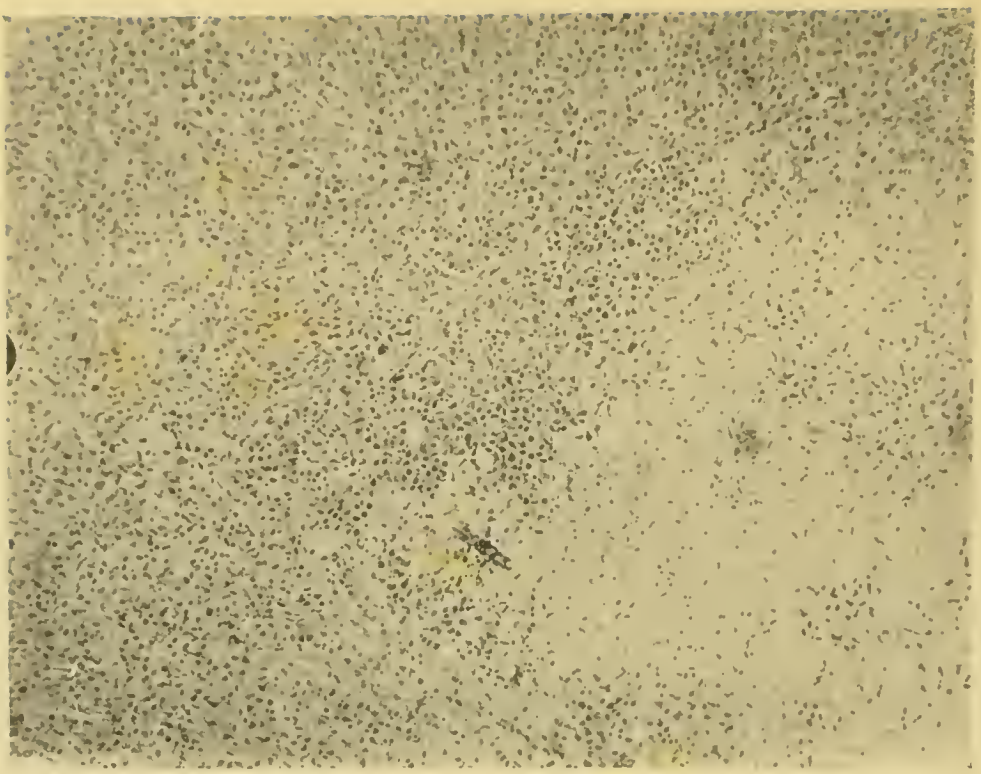


Fig. 10.—Lympho-sarcoma, before treatment.

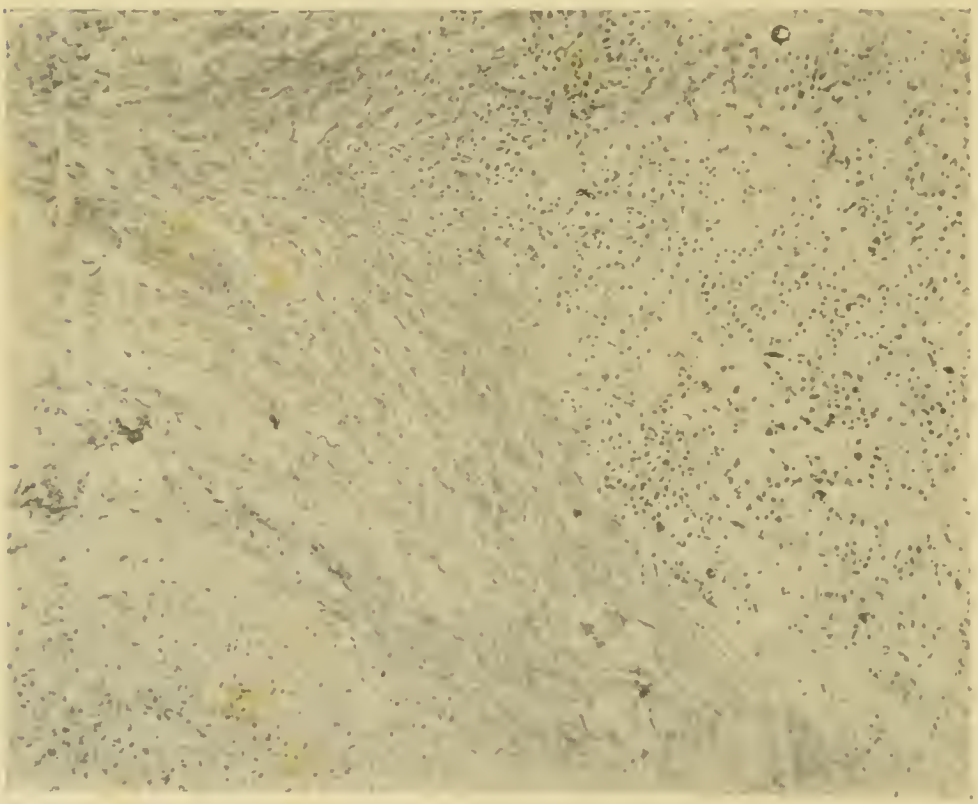


Fig. 11.—The Same, six weeks after treatment.

fibrous tissue seems to be subsequently formed. As has been mentioned above, data on this subject are very difficult to obtain from the human being, and until careful comparative results are worked out on animals a large gap remains in our knowledge of these matters. Examination of the diseased tissues before and after the radium treatment wherever possible is being made, and considerable good will be done by collection of these results. Figs. 10 and 11 show a section of a lympho-sarcoma before and six weeks after treatment. Figs. 12 and 13 show the changes effected by γ-rays, Fig. 12 being before treatment and Fig. 13 after two applications, respectively twelve and six weeks previously. The case was one of very advanced carcinoma of the cervix of the columnar-celled type.

Physiological Action of the Rays

The rays are at present employed for irradiation of localised areas only, and with the amount we use at present no general effect is directly produced, though, if a dose sufficient to cause a burn is given, the pain or sepsis resulting from this may have far-reaching effects. The physiological effects of the internal administration of radium or its emanation are dealt with in Chapter II.

Locally, the only visible effect of the β-rays is to produce an inflammatory reaction which commences a few days after the application, and the bigger the dose of rays that has been given the shorter this period. Epilation occurs with large doses of β-rays; it is permanent if a large dose is given or if moderate doses are repeated several times. The same may be said in regard to the action of β-rays on the other glands of

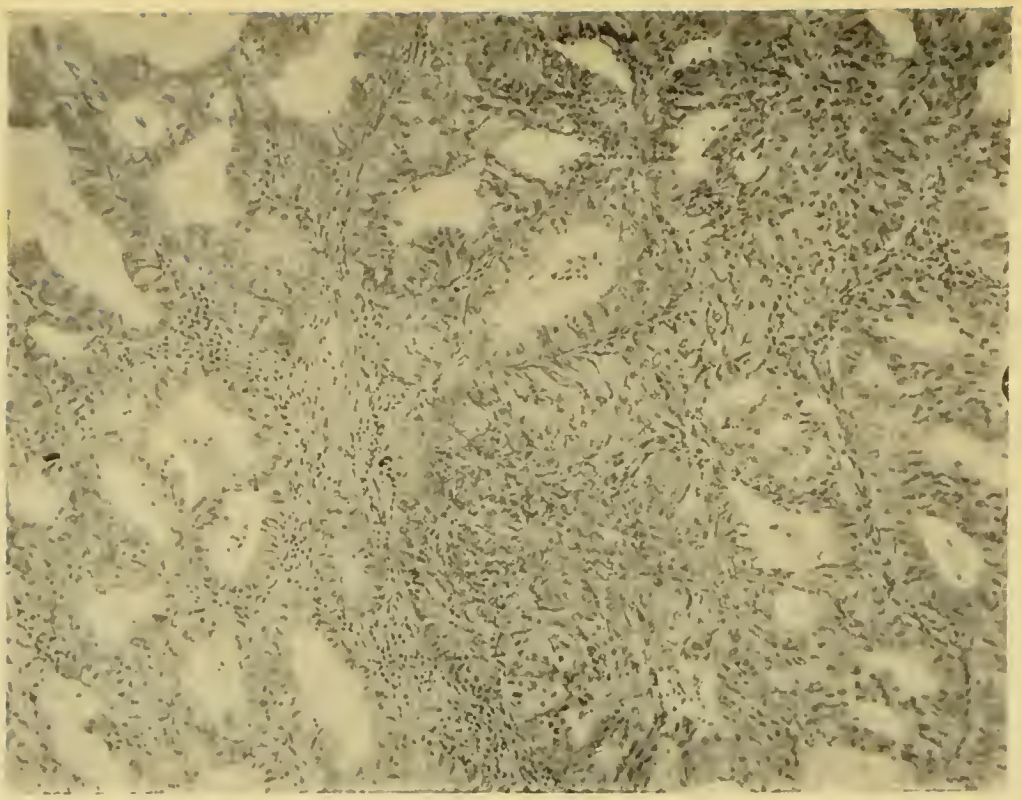


FIG. 12.—Carcinoma of Cervix, before treatment.

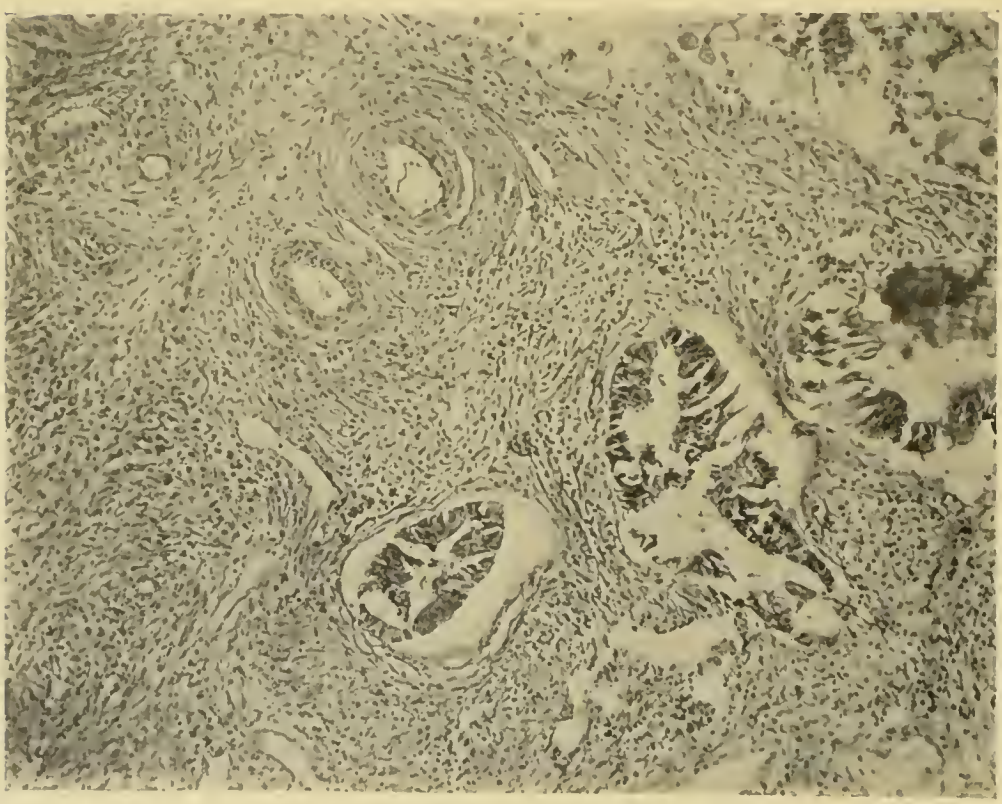


FIG. 13.—Carcinoma of Cervix, after two treatments.

the skin, namely, they are destroyed temporarily or permanently according to the dose.

With the γ-rays it is different. The latent period before any change is observed is now between two and three weeks, if the dose is just sufficient to cause an erythema in the skin; an inflammatory reaction then occurs and is accompanied or followed by epilation and destruction of the sweat and sebaceous glands. A bigger dose shortens the latent period and causes vesication and still larger doses ulceration of the skin; this latter may soon heal, but if the dose has been a very large one, heals only very slowly and with the greatest difficulty, leaving a scar that subsequently becomes covered with teliangiestases: these, in fact, are liable to occur in any γ-ray scar when ulceration has been produced, but there is much less likelihood of their forming in a β-ray scar. The epilation is permanent with a large dose even when this is insufficient to produce a scar, or with a smaller dose if the application is repeated several times.

A pigmentation of the skin occurs after the erythema subsides, or, if the dose is just insufficient to cause a visible erythema, it may appear some four or five weeks after the application. It is much more marked in dark than in fair individuals, and subsequent applications increase its intensity, but it gradually fades away when they are stopped. This, also, is not seen with β-rays.

Deep glands will be affected as well as superficial; for instance, the functions of the testicle and ovary may be destroyed by an efficient irradiation of these organs.

After an application of filtered radiations a secondary reaction is sometimes seen, quite separate from the first; it does not appear until five or six weeks after the

application, and seldom consists of more than erythema. It only occurs in a small proportion of cases and very little is known about it. It is possible that it may be due to secondary rays which are incompletely filtered.

Action in Disease

When the rays, whether β or γ, cause a tumour to absorb rapidly, a considerable effect results on the general health, and there are, for a few days, malaise and discomfort, which, however, are soon counteracted by the improvement caused by the relief from pain and the arrest of the development of the growth. Profound effects are sometimes seen, but no case has been observed in which they were sufficient to endanger the patient's life.

The effect of these rays on a neoplasm depends, at any rate to some extent, on a vital reaction of the tissues, and there seems to be a stage of the disease when this is lost and the tissues fail to react. This may account for the very different effects seen to result from early and from later treatments in some cases: the radium having failed to cure the disease completely, the resistance of the patient has diminished, and with subsequent doses no useful effect is produced. The nature of this vital reaction is not known, but the existence of the latent period points to the probability that some chemical substance is gradually formed, which damages or destroys the cells of the growth.

The effect on inflammation is to diminish or remove it, probably by stimulating the tissues to resist the action of bacteria, and partially also by the germicidal action of the β-rays. Thus, simple ulcers may be

caused to heal when they have resisted other treatments, and the same may be said of tuberculous sores.

Action on Bacteria

Chambers and Russ[1] have performed a valuable series of experiments throwing some light on this subject. They find that the α- and β-rays have a distinct bactericidal action, but are unable to observe any with the γ-rays. It seems to us possible, however, that there may be a latent period to the γ-ray action, and though one generation of bacteria might live insufficiently long for this to manifest itself, it might be shown in subsequent generations if the observations were carried on long enough. However, no effect was observed from a week's exposure to the γ-rays from $7\frac{1}{2}$ mgrms. of radium bromide, while with β-rays a complete lethal effect was obtained in six hours. The action of the α-rays and of the emanation is more powerful still in this direction. On the other hand the action on opsonins is not nearly so powerful as the action on bacteria, and that on phagocytes is less still. They also find that the action of the emanation itself is much more powerful than the action of the rays from it.

[1] *Arch. Middlesex Hospital*, vol. xxvii. p. 29.

CHAPTER IV

APPARATUS AND METHODS OF APPLICATION

The appliances for internal treatment by emanation, etc., have been described in the chapter dealing with those methods.

The apparatus for making various local applications with radium must vary to a certain extent with each case, though the same radium applicator can be so constructed as to be very generally useful. With skin diseases, where it is desired to treat evenly a large area, it is obviously of advantage to have the radium spread on a flat surface. The best way of doing this is to convert it into an insoluble salt, spread it evenly on an applicator of suitable size and shape, and cover it with some special protective varnish, which will be impervious to moisture and gases, and which should be hard and resist the action of most chemicals. The intensity of the radiation will depend upon the amount of metallic radium present, so that there is no objection to using impure radium salts so long as the bulk of the impurities is not so great as to cause the salt to lie in a thick film. In dealing with these applicators we require to know, in order to calculate the dose—

1. The amount of metallic radium per square centimetre.

2. The thickness of the film of varnish and the amount of rays it will absorb.

If, as is usual, the radium is coated on a backing of metal, we shall also be using secondary rays from this unless the varnish absorbs them or we interpose something between the varnish and the skin to do so. It seems advisable in most cases to use a thin sheet of aluminium[1] as a filter in order to ensure that the β-rays used will penetrate sufficiently into the skin, as the very slow β-rays, which are stopped by this aluminium, would otherwise be liable to be absorbed by the superficial layers of the skin and to cause excessive inflammatory reaction without proportionate benefit. It is usual also with most of the workers in this branch of the subject to use, in addition, several layers of black paper, in order to absorb the secondary rays from the metal. In all probability, however, the thin layer of aluminium is sufficient to absorb the harmful rays in this particular method of treatment—β-ray treatment—and though the aluminium itself gives out some secondary rays, these will not be sufficient or penetrating enough to cause any trouble if a thin layer of gutta-percha tissue or other protective is used over the radium applicator: this precaution is also advisable for cleanliness and for the preservation of the applicator itself. When it is desired to treat a surface with γ-rays, a filter of lead is used instead of the aluminium. In this case it is certainly advisable to filter off the secondary rays with a couple of millimetres of paper or lint.

The radium is also sometimes spread upon cloth and coated with varnish, and this forms a beautifully flexible but very fragile applicator, while the use of filters of any sort diminishes its flexibility considerably.

The metal applicators are made in various shapes and sizes, but the square ones will be found more

[1] Say, 0·25 mm.

generally useful, as, although most lesions are round, the square applicator can be so much more easily used for a large surface by treating a number of squares successively. Of course in big institutions, where a great quantity of radium is on hand, a large number of circular applicators of different sizes will probably be

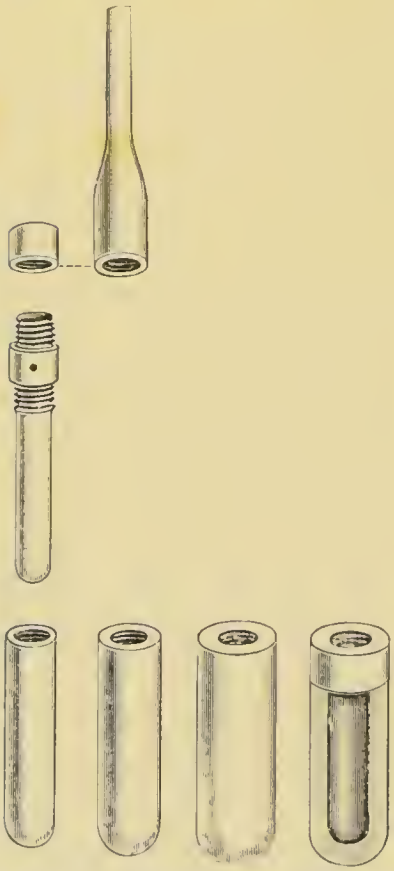


Fig. 14.—The Author's Tube and Accessories

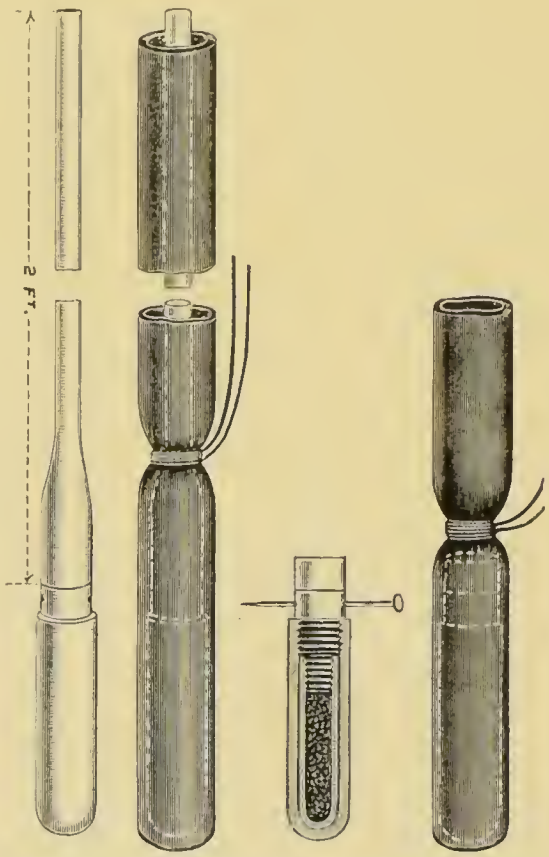


Fig. 15.—The Author's Tube arranged for use.

found more convenient. It must be mentioned here that these flat applicators may also be used in the treatment of deep growths, a large number of them being applied simultaneously to different portions of the skin, so that their rays cross in as many directions as possible. Another method which is more generally useful, because it allows of the employment of almost indefinite quantities of radium, is referred to subse-

quently,[1] and though a similar quantity of radium could be used on flat applicators, these would need to be specially made, as those ordinarily used do not contain the salt in a sufficiently concentrated form.

The use of tubes was the earliest method for the application of radium rays to the human body, and the modern patterns of tube have every advantage for the treatment of deep diseases, while they can easily be used for superficial diseases, especially if filtered rays are advisable. To those working at deep diseases, malignant growths, and so on, these tubes should afford the best form of apparatus, and the author has designed a form of tube which is very compact, and allows of the use of different forms of filter and different dispositions of the radium tubes. This apparatus is illustrated in Figs. 14 and 15. Fig. 14 shows the inner radium tube and the cases which screw on to it. Fig. 15 shows the same tube with a 1 mm. case on it, and also the tube ready for use in two different forms. Fig. 16 shows apparatus for using two or more radium tubes screwed together in different ways. In A the active portions of the tubes are together forming a continuous radio-active line; in B there is an interval between the radio-active parts. From Fig. 15 it will be seen that the radium is contained in a small inner tube of platinum $\frac{1}{2}$ mm. thick; into this is screwed a special stopper, and this stopper is then soldered in by means of gold solder. On the stopper

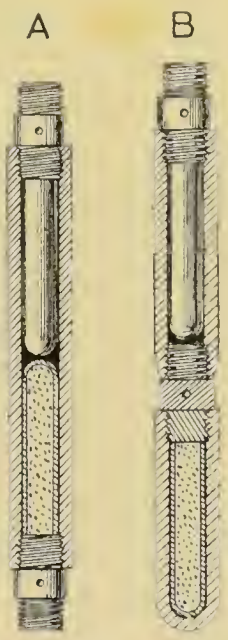


FIG. 16.—The Author's Tandem Applicators.

[1] Page 60.

are cut two further threads with a space between them, through which a hole is drilled for the insertion of a pin to obtain easy leverage for screwing the screens off and on. The screens are tubes which fit on to the lower thread, and in the illustration (Fig. 14) are four in number—three of different thicknesses of platinum, and the fourth of platinum with one half cut away, this last being used to cut off considerably more rays on one side of the tube than on the other. The uppermost thread is made to take either a platinum cap or a long silver rod. The whole apparatus is then tied into a specially made pure rubber tube with a closed end. The rubber is used partly with the object of cutting off secondary rays from the metal, and should be pure rubber and free from metallic substances, but it also serves to protect the tube and keep it clean. That the rubber is fairly effective in cutting off the secondary rays the author has proved by experiment, 1 mm. being sufficient almost entirely to suppress them, while it gives no appreciable secondary radiation itself.

Now this apparatus can be used either externally or internally, in cavities in the body or inserted into growths : screwed on to the rod the apparatus is used in the mouth, the pharynx, the œsophagus, the rectum, and other positions. The œsophageal application will be first dealt with as being rather a difficult one and typifying the method of using the tube attached to the end of the silver rod. The cases in which radium is employed in the œsophagus are usually carcinomata, causing stricture, and these are generally found to involve the œsophagus for several centimetres of its length ; therefore, one of the arrangements illustrated in Fig. 16 will often be found of use. If it is possible to pass the radium tube right through the lumen of an

annular growth, it will be as well to use the form in which the active portions of two of the tubes are close together, thus forming a long radio-active rod; in

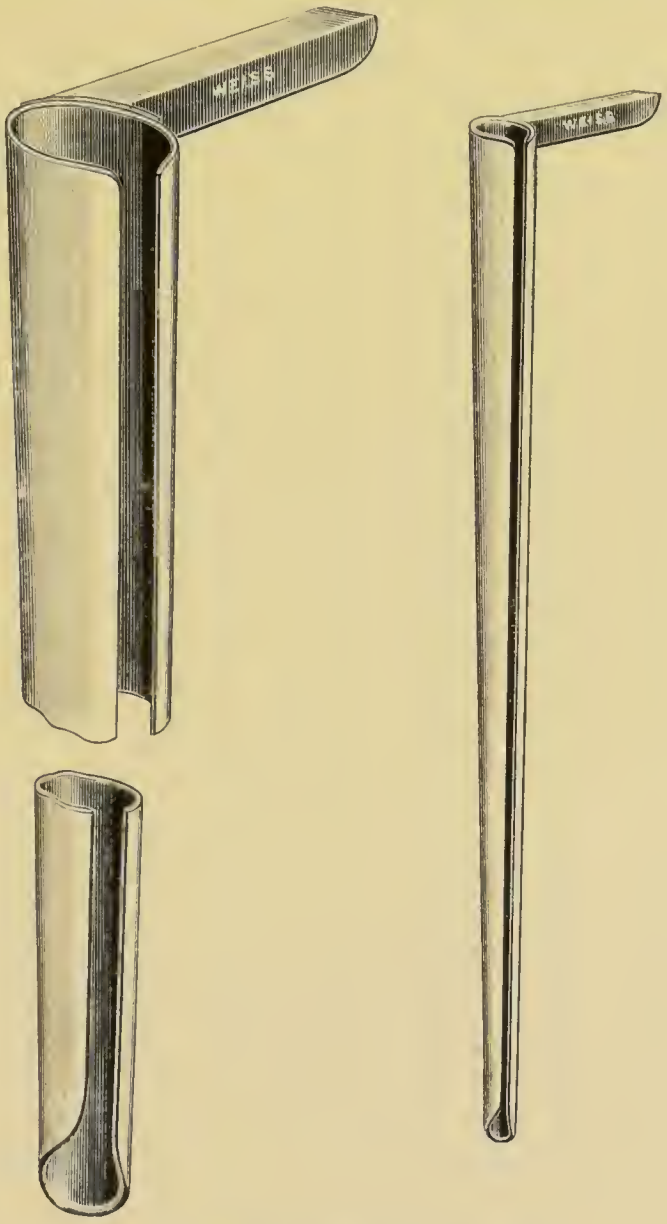


FIG. 17.—William Hill's Split Tubes.

other cases it may be better to use that form in which there is a gap between the active portions of the tubes, and move the rod up or down a little, after a certain fraction of the total application, to expose the parts

omitted at first. The best method of applying radium to the œsophagus is to introduce it by means of the œsophagoscope, and the tube invented by Hill with a lateral slot along its whole length (Fig. 17) is most useful for the radium application, as the lateral slot allows of the œsophagoscope being withdrawn without disturbing the radium apparatus (Fig. 18). It is possible by this means to place the radium exactly in position, but the difficulty comes when the œsophagoscope has been removed; it is then necessary to bend the silver rod at the pharyngeal angle in order that the patient may be able to get his head into a reasonably comfortable position. We have been able to prove that, during this bending, however carefully done, the radium tube may often be displaced 3 or 4 cms. up or down. Movements of the patient's head also cause a considerable excursion of the radium tube; therefore, a screen examination with the X-rays is made, the patient swallowing some bismuth and water which outlines the stricture quite distinctly, and by this means the position of the radium tube can be checked with great exactitude. Figs. 19 and 20 show a radiogram of a case in course of treatment in this way. Three tubes

Fig. 18.—Application of Radium to a Growth in the Œsophagus.

are being used, two tandem (as in Fig. 16) and the third secured only by the rubber tube which encases the whole

FIG. 19.—Radiogram of an Œsophagus with Radium Tubes in the growth : Posterior View.

apparatus. Fig. 19 is a posterior view and Fig. 20 is taken in the right antero-lateral oblique position. The danger and, in many cases, the uselessness of the blind method of introduction is shown in Fig. 21, in

which the dotted lines represent false positions which

Fig. 20.—Radiogram of an Œsophagus with the Radium *in situ* : Right Antero-lateral Oblique View.

the radium tube may assume—positions where the rays would cause damage to healthy mucous membrane

and have very little effect upon the main part of the growth. Fig. 22 shows the apparatus as it should be when in position. It is generally necessary to dilate up the stricture to some extent before applying the radium. In order to render the silver rod more flexible it is first heated to redness and cooled before use.

In applying radium to the tonsil it will be found useful to have two or three tubes tied side by side as in Fig. 23. In order to keep the tongue away from these and prevent it getting as large a share of the rays as the growth itself, thick pieces of pure rubber tubing are fixed behind the radium tubes. A somewhat similar arrangement will be found useful for growths high up in the rectum or the sigmoid, but if there is a stricture the tubes are placed tandem, so as to lie in the stricture.

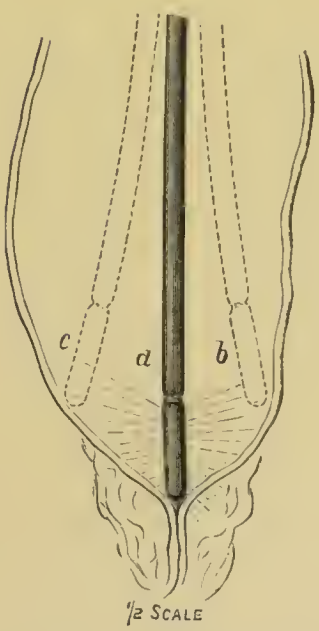


Fig. 21.—Bad Positions.

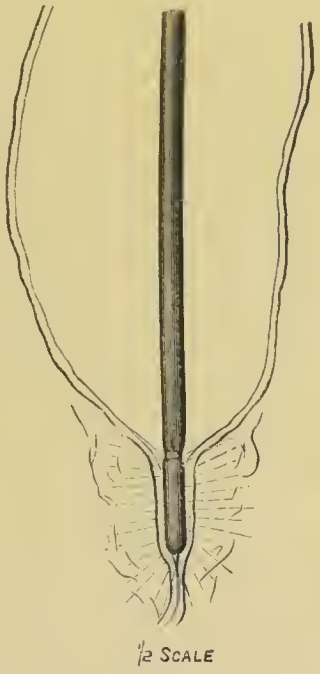


Fig. 22.—Good Position.

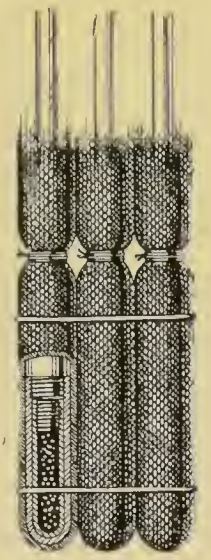


Fig. 23.—Tube Apparatus arranged for the Tonsil or similar situation.

In the bladder the same arrangement is used as for the œsophagus, or the radium tube may be inserted in the end of a soft catheter, an opening in the catheter being made below the radium to allow the urine to drain off.

For insertion into the substance of growths, the tube is arranged as shown in Fig. 15, right-hand side, but the rubber is cut off close to the silk thread which ties it. The radium being sealed in by metallic solder, there will be no harm in boiling the tube in order to sterilise it; great care must be taken, however, not to let any mercury lotions come in contact with the platinum, as they would seriously damage it.

In growths of the floor of the mouth or under the tongue, the method adopted is to pass several stitches of coarse silk through the tongue and bring these out through the cheek or lower lip so as to fix the tongue securely. The radium tubes are then laid in the growth and the stitches tied so as to fix them securely in a position in which they will, if possible, be completely surrounded by the growth. If it is not feasible to get the radium completely enclosed in growth, and healthy tissue has to be in contact with it on one side, a pad of cotton-wool or some other substance which will not emit secondary rays is used between the radium and the tissues on this side, so that, by increasing the distance from the rays, the dose, where it is not required, is considerably diminished.

To apply the radium to the upper part of the pharynx and posterior nares, a Belloc's sound is first passed through the nose into the mouth, and the radium tubes are then drawn up through the posterior nares on the piece of silk so introduced.

In the lower part of the pharynx the best

method (suggested by Dr. William Hill) is to tie the tubes on to the side of a gum-elastic bougie, which is then passed for some distance into the œsophagus and serves to steady the radium apparatus in the position required. This tube is best introduced by the large direct-vision pharyngoscope shown in Fig. 24.

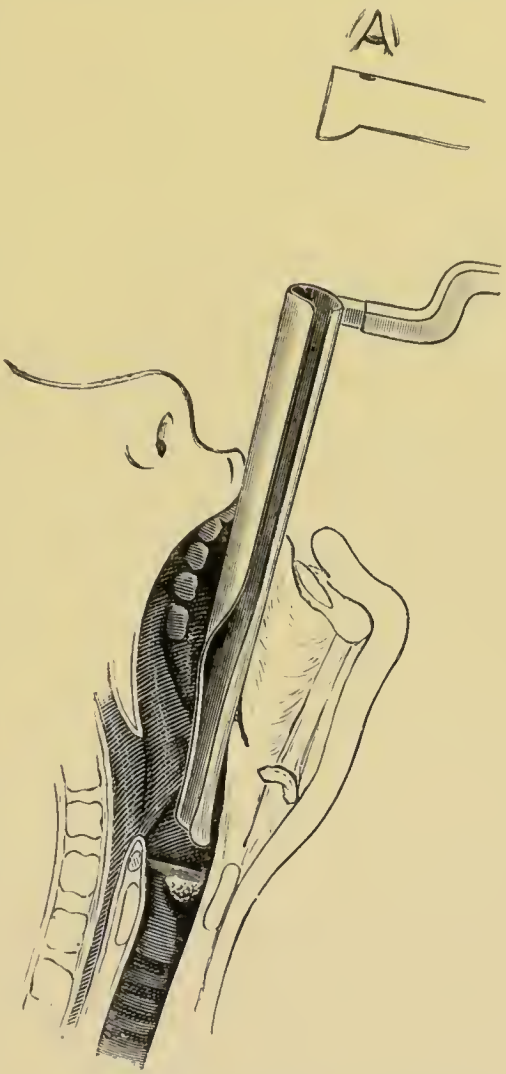


Fig. 24.—Method of introducing Radium into Pharynx or Larynx.

For the vagina, the small tubes are inserted in the required position and kept in place by gauze packing. For the uterus, the cervix is dilated and the tubes placed in the uterine cavity, care being taken that the largest can be easily removed.

For the rectum low down, the tubes may be used in the same way, but in growths higher up the silver stem will be found invaluable. In growths in the sigmoid or high up in the rectum the use of a sigmoidoscope for the introduction of the radium is essential, the instrument being inserted as far as possible and the radium then passed through it to the correct position, the illuminating stem being of course first removed.

For the vulva or anus, the tubes are simply laid in position, the buttocks strapped together, and the patient enjoined to lie still during the application.

Another tube apparatus which, we understand, is feasible, is with the radium in a very thin platinum tube, the ends of which are sealed; one or more of such tubes could be enclosed in a box of suitable thickness for the filtration required. If a filter of, say, 0·1 mm. of platinum were required, and this were the thickness of the inner tube, the outer frame would be made with a window. Fig. 25 is an illustration of such an apparatus.

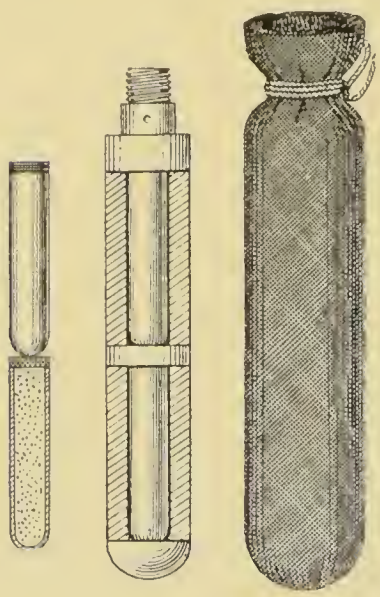


Fig. 25.

In employing very large quantities of radium, for instance a gram, to comparatively small areas, the best method is to make a block of felt (this is better than wood) of a thickness calculated according to the time of the exposure, and so to dispose the radium tubes on the surface of this block that an even amount of rays will be obtained from it when it is placed upon the skin. The author has found it possible by this method to get absolutely even action with a gram of radium, the pad used being 12 centimetres square.

CHAPTER V

TREATMENT OF SUPERFICIAL DISEASES

In diseases of, or just beneath, the skin, as it has already been explained, flat applicators will be of more general utility than tubes ; these latter, however, can be used, and it is possible to get a perfectly even action by carefully calculating the dose, using several tubes and arranging the position of these so that they can be altered after one-half of the exposure and then re-arranged to neutralise any possible inequalities. It is often a good plan to replace them at right angles to their former position. It is also possible with very short exposures, with thin filters, to move the radium about during the exposure, and in this way to act more evenly on the surface ; the operator, however, must avoid any damage to his own hands by using some sort of holder.

Preparation of the Surface to be Treated

It is advisable and, when a thin filter or none is being used, absolutely necessary, to remove from the surface all crusts, discharge and moisture, and then to stop any bleeding caused by this procedure. If it is required, as it often will be, to give to the diseased area a larger dose than the surrounding skin, and a flat applicator is being used, a piece of lead, coated

with rubber with a hole cut in it the size of the lesion to be treated, is fixed firmly in position on the skin, the rubber preventing secondary radiations from the lead from reaching the skin; the thickness of the lead will depend on the amount of filtration used for the radium rays. If this latter does not exceed 1 mm. of aluminium, 1 mm. of lead will suffice to protect the skin. It is, of course, only necessary to reduce the amount of rays falling upon the healthy skin to within the dose which the normal parts will stand; there is no necessity to keep the rays off entirely. If the lesion is too large to be covered by a single applicator, it will be best to have a square applicator and to cover the surface in sections, which can easily be marked off with a skin pencil; care must be taken not to overlap. When it is necessary to use thick filters for external applications, tubes will be found more convenient.

Inflammatory Lesions of the Skin and Mucous Membranes

Many of these can be treated with great benefit by β-rays of radium. It is needless to use a thick filter in these cases, and 0·25 mm. or 0·5 mm. of aluminium will usually be found ample. The exposures should not be very long, if a large quantity of radium is used, but in these diseases it will also be found possible to get good results by long applications with a small quantity of radium. The actual time of the application for a certain weight of radium will depend considerably upon the size of the applicator over which it is spread: a thinly spread applicator is the most economical, and radium spread over a surface and

coated with varnish as in the apparatus so extensively used in Paris is the best type. In order to protect the apparatus, especially if it be used without a filter, it is advisable to wrap it in a thin piece of guttapercha tissue or other protective material, otherwise continually wiping the surface of the varnish to clean it will in time wear it away and expose the radium granules.

Chronic eczema, which has proved rebellious to other treatments, has often been cured by radium treatment; in the weeping variety all crusts and discharge are removed from the surface before the application, and the dose should be one which would just produce a mild erythema in the healthy skin. If the patch to be treated is very inflamed and tender it will be best to fractionate this dose, and give about one-eighth of it twice a week; it will be noticed that this is a slightly bigger dose than can be given when the application is done all at once, for in this latter case it is inadvisable to repeat the application before five or six weeks' time. In some cases X-rays and in others radium will be found more effective.

In psoriasis disappearance of the patch treated is almost invariably obtained and also amelioration or disappearance of untreated patches, but treatment by radium will not prevent the recurrences which are so common in this disease.

In lichen planus, acne rosacea, and lupus erythematosus very excellent results have been obtained; sycosis has been successfully treated by giving a sufficient dose to cause epilation, but in this condition radium has probably no advantage over X-rays. In molluscum contagiosum, xanthoma and sebaceous adenoma the results have also been successful.

In tuberculosis of the skin, a similar method to that used for eczema has answered admirably. Lupus vulgaris and lupus verrucosus are, on the other hand, less amenable, but good results can be obtained especially in combination with other methods of treatment, such as scraping, cautery, etc.; in this condition all the nodules must be thoroughly exposed, and a good method is to use a plaster containing salicylic acid for a week or so before the radium treatment is commenced, or to rub the surface with liquor potassæ, and wash it off again just before the treatment. Wickham and Degrais advise the use of very strong doses in this condition in order to get the caustic action of the radium, but this is unnecessary in most cases and is liable to leave ugly scars, besides being extremely ineffective. These authors record comparatively poor results in lupus vulgaris, which are undoubtedly due to the use of unfiltered radiations. The experience of those who employ proper screens is quite different. Barcat [1] concludes that the best filtration to employ in this complaint is one-tenth of a millimetre of lead or one millimetre of aluminium. Beneficial results can, however, be obtained with half a millimetre of platinum. General treatment by open air and good food must be insisted on. Mesothorium has also been used with success in lupus vulgaris (see Appendix).

Syphilitic lesions can often be given just that extra stimulus, in order to make them heal up, which is occasionally lacking when the ordinary treatments only are employed. The dosage here again is the same as that for eczema or slightly larger.

In some cases refractory ulcers can be caused to

[1] Barcat, "Précis de Radiumthérapie," Paris, 1912.

heal by radium applications. The rays filtered through $\frac{1}{2}$ mm. of platinum give quite good results in these cases, but it is probably equally satisfactory to use a filter which absorbs less of the rays, namely, $\frac{1}{2}$ mm. of aluminium. It is essential in these cases to see that the general treatment is carried out satisfactorily; for instance, the proper bandaging of the leg in a varicose ulcer and the treatment by anti-syphilitic remedies in a gummatous ulcer.

A combined method of treatment must be mentioned here which will probably prove very useful in the treatment of some ulcerations, and that is, causing zinc or mercury ions to enter the ulcer by a galvanic current and then immediately applying the radium; the intense secondary radiations from the deposited ions have a powerful therapeutic effect[1] apart from that of the ions themselves, which are extremely useful in these conditions.[2]

Leucoplakia is very often cured by radium applications, even when it has resisted all other methods, but filtered radiations must be used if the result is to be lasting: $\frac{1}{2}$ mm. platinum is sufficient.

Cicatrices

It is always observed by radium therapeutists that, in treating a region in which there is an operation scar, if this scar is recent it is considerably softened and the fibrous tissue does not contract up subsequently in the usual way, while if the scar is old the amount of contraction is diminished and the parts fixed down by it

[1] Hernaman-Johnson, *Proc. Roy. Soc. Med.*

[2] Finzi, "Treatment of Ulcers by Ionic Medication," *Proc. Roy. Soc. Med.*, May 1909.

considerably loosened. It follows that radium treatment will be very useful in diminishing the evil effects of bad cicatrices and in preventing these from forming. For instance, after a bad burn the amount of cicatrisation is often very great. As soon as such a wound has healed over, radium should be applied in order to prevent the severe and disfiguring effects which result when the fibrous tissue contracts if it is left alone. In cases where the contraction has already occurred the results can be alleviated. The γ-rays appear to be the most useful, but probably the penetrating β-rays have some value. A $\frac{1}{2}$ mm. platinum screen will be found very suitable, and whether tubes or flat applicators are used will depend on the shape of the scar.

Pruriginous Affections of the Skin

In these, radium is of very great value, for it is often the only known means of controlling the trouble, short of dividing the nerves to the affected area. The β-rays appear to be the most valuable in this condition ; in what way they act is not known, though in some cases, where there are visible changes in the skin, as, for instance, in pruritus ani and pruritus vulvæ, these are caused to disappear. The best applicator for these conditions on large skin areas is naturally the flat varnish apparatus, but tubes can be used provided the filter is not too thick, and in the anus and the vulva the conformation of the parts makes a tube the easier applicator.

Painful Affections of the Skin

In these, radium is of great value, especially in the neuralgia which sometimes follows herpes zoster. The

anæsthetic effect seems to be exerted here, as in pruritus, by a direct action on the nerves. In most of these cases a filter is unnecessary, but if the affection proves refractory to the total radiations, a filter of one-tenth to one-fifth of a millimetre of lead should be used.

Hypertrophy of Normal Tissues

Hypertrichosis

This common and distressing complaint has rarely been treated with radium. The author has treated one case in which electrolysis had been previously used, and had been followed by keloid, without the hairs being completely destroyed, and in this patient, in whom the hairs were situated underneath the chin, a very successful result has been obtained without any scarring at all, the keloid also having disappeared. The hair has not returned nearly two years after the application. In this case a filter of 2 mm. of platinum, 1 mm. of rubber and one layer of lint were used, and 300 mgrms. were applied for four hours. A similar case gives promise of equally hopeful results. It has also been observed in many cases of other diseases which necessitate applications of radium to the neck, that epilation follows, which is not permanent with moderate doses but seems to be so after a few large doses. Even where the epilation is not permanent the hair does not return for many months, so that this method might be employed at long intervals; very great care, however, must be taken not to give too large a dose, especially considering the disastrous results that have followed in some cases treated for

this complaint with X-rays. Of course in these cases spread radium will be more useful than tubes in order to get an even result. A thick metal screen is a necessity, as it appears to be the γ-rays which cause the epilation. The method is an expensive one and is still in the experimental stage.

Hyperhidrosis

X-rays are so satisfactory in this condition that, although radium would probably have the same effect, the difficulty of getting even action over a large area will lead to a continuance of the use of the former. γ-rays would be used if radium were tried.

Hairy Moles, Pigmented Moles, etc.

These are very favourably influenced by radium, but if the lesion is very small it would be better to use carbon dioxide snow. A thin filter should be used in treating this condition and a large dose given, the surrounding parts being protected.

Benign Growths affecting the Skin

PAPILLOMATA

Radium has a very marked influence on these growths, and it must be remembered that they include warts and corns besides the soft papillomata. One dose is very often sufficient to completely cure papillomata that have resisted caustics, etc., for many months, but it is advisable to give a second dose as prophylactic.

It may be said that in papillomata radium is one of the best, most painless and most successful treatments that there is. Abbe[1] has recorded successful results in papilloma of the vocal cords.

Corns

In this painful form of papilloma radium is of the utmost value. In the soft variety the pain soon disappears and the growth gradually shrinks up, leaving, as a rule, no trace of having existed. In the hard variety the pain also soon disappears, though the corn apparently remains in a somewhat softer state than before. About six weeks after the application the skin which contained the corn peels off, leaving a healthy surface and again no trace of its former presence.

As a rule, one application is sufficient for a corn, but two or three may be needed. Filtered rays must be used, especially in the hard variety, and we employ 0·5 mm. of platinum. The dose is rather more than would produce erythema in the healthy skin, and it will usually be found advisable to use a tube and, during the second half of the exposure, to place it at right angles to its former direction, in order to obtain a more intense action in the centre of the corn.

Warts

The application is made in the same way as with a corn. The wart gradually flattens and disappears—it does not usually peel off like a hard corn. The method

[1] *Med. Rec.*, N.Y., 1912, vol. i. p. 703.

is especially useful for single warts on the palmar surface of the fingers, and is quite painless. It is also very useful in warts of the scalp.

When the warts are multiple it is unnecessary to treat all the lesions, as, if enough of them are caused to disappear, the others will also undergo regression.

Gonorrhœal warts also react well to radium treatment.

RHINOPHYMA

This disease, which appears to be an over-growth of the sebaceous glands of the nose or a benign neoplasm of these glands or of the skin, is very readily influenced by radium rays, and the nose can be brought back almost to a normal condition.

ANGEIOMA

As this is a benign growth which generally affects the skin, it will be dealt with here. Radium has been found most useful in the treatment of this, and although in a certain class of case it has been replaced by the more rapidly-acting carbon dioxide snow, it is still the treatment which leaves the least scarring, which is the least painful, and which will cure some angeiomata which cannot be cured by snow. Especially is this latter remark applicable to deep angeiomata in young babies, which only involve the skin over a small portion of their extent: the way these disappear under comparatively small doses of radium rays is truly wonderful.

Port-Wine Marks

The results of treating these are not good, whatever method is used, but radium treatment is the best available. The stain is considerably diminished in colour, more so if its original tint was very deep, but great care must be exercised to avoid giving overdoses and producing white scars and telangiectases; one must be content with merely reducing the colour of the stain until it is almost unnoticeable, as excessive treatment causes scarring, which is even worse than the original nævus. If the nævus is pale in colour it will probably not respond readily to treatment. A good plan, in treating port-wine marks, is to use a very weak preparation of radium and apply it for a very long time—a pitchblende plaster worn every night causes no inconvenience, and after a year or two distinct improvement will probably be seen—either no filter or only a very thin one is used, and spread preparations have a very great advantage over tubes, especially if the radium is spread over a surface large enough to cover the whole nævus: if the applicator is too big for the stain the healthy tissue around is protected by lead foil.

Pigmented Nævus

This much resembles port-wine mark except that it does not usually occur in the face. The remarks with regard to the latter apply equally to the former condition.

Cutaneous Nævus (Strawberry Mark)

This is treated so easily and successfully with carbon dioxide snow that radium will only be required for it if it is important to obtain a result with the minimum of scarring. As there is usually no hurry, if the patient's parents care to go to the extra expense the radium is better, for it is a painless treatment and certainly leaves less scar. As this condition usually affects the skin to a depth of several millimetres it will be advisible to use a thin filtration, say $\frac{1}{2}$ mm. of aluminium, and, owing to the shape of the lesion, tubes can usually be employed as satisfactorily as plaques.

Subcutaneous Nævus

This responds quite well to moderately filtered radium rays, especially in young babies, and though in some cases excision or electrolysis may be preferred, radium will usually be found very satisfactory. The filter should be about $\frac{1}{2}$ mm. of platinum or 1 mm. of lead.

Spider Nævus and Telangiectasis

These are usually best treated by electrolysis.

URETHRAL CARUNCLE

Urethral caruncle has been treated with success by radium rays, but in the only case the author has treated in this way the result was not successful. A

tube must be used and inserted into the orifice of the urethra against the caruncle if it involves the urethra.

KELOID

This disease may be divided into two forms, in both of which admirable results are obtained; one form grows fairly rapidly, producing a large swelling which is often painful, and the other causes a comparatively slight swelling of an operation scar and is only unsightly and very seldom painful. Both of these types can easily be cured by radium, but especially the first. Pain rapidly disappears and the swelling gradually diminishes. It is seldom necessary to give a caustic dose, a mild reaction alone being aimed at; a filter of $\frac{1}{2}$ mm. of platinum is very suitable for these cases, and, as a rule, tubes are the best form of applicator, for the disease most commonly occurs in an operation scar which is linear and its stitch holes which are punctiform.

Malignant Growths of the Skin.

Rodent Ulcer (including Epithelioma of the Sebaceous Glands)

Here radium has one of its most important uses. Treated by suitable methods and sufficiently early, the disease can be eradicated in practically every case. Whether these are cures we cannot yet be certain, but many of them have lasted some years without recurrence. Owing to the penetrating character of the radiations it is probable that they will destroy outlying cells of the growth better than other methods, and recurrences,

as may be expected, are rare. Though superficial cases have been healed by the application of unfiltered rays and small quantities of radium, it is much better to use large quantities and a moderate filter ; $\frac{1}{2}$ mm. of platinum gives very satisfactory results. The advantage of the latter method is that the deepest parts of the growth are reached by the rays instead of a mere surface healing taking place, and the retrogression is obtained with far less reaction than when naked radium is used. In any case, at least two prophylactic doses must be given after the growth has disappeared completely to the naked eye. It has been found that after the growth has apparently disappeared the scar still contains neoplastic cells, and unless these are quite eliminated no cure can be expected : every remnant must be absolutely eradicated, then and only then can success be expected, and the same applies throughout to the treatment of malignant disease. The small amount of scarring, even after a big growth has been removed, is almost incredible, and is less than by any other treatment. Treatment by unfiltered radiations yields by no means such good results, and it has fallen to the author's lot to heal by filtered radiations a case which had previously proved refractory to large doses from unscreened radium.

Superficial Cancer

1. *Primary Growths*

Malignant growths in the skin are almost always squamous epitheliomata, though melanotic sarcomata and a few other forms occasionally occur. The first is a type of neoplasm which does not respond very readily

to radium, though by giving caustic doses it can be got rid of with a fair degree of certainty in early cases. However, it is still best, in order to be on the safe side, to excise the growth and the glands draining the affected area, leaving radium tubes in the wound at the time of the operation for a few hours as a prophylactic ; care must be taken not to give too large a dose or a sinus will remain. The filter should be 2 mm. platinum ; with a tube containing 100 mgrms. of pure radium bromide and with this filter the dose is about five hours. The radium apparatus is tied into a piece of rubber tubing and sterilised : the rubber tube is used to pull the radium from the wound at the right time, and may then be replaced by a drainage tube if the surgeon so desires. If this disease is treated with radium alone the dose must be large and the glands treated prophylactically, even if not enlarged : the filter is the same as above.

Epithelioma of the mucous membranes, anus, vulva, etc., will be dealt with in the next Chapter.

Melanotic sarcoma disseminates very rapidly, and if anything can be done it is best to excise the primary growth to save time, following this by prophylactic treatment. In hopeless cases radium may be used to give relief. Owing to the frequency with which secondary deposits in the lungs occur with this growth, it is most advisable to treat the chest with radium rays if a sufficient quantity is available, or with X-rays if it is not. The writer has also treated a recurrent spindle-cell sarcoma in the skin, which disappeared completely.

2. *Secondary Growths*

See Chapter VI.

CHAPTER VI

TREATMENT OF INTERNAL DISEASES

Benign Growths

Most benign growths, deeply situated, are very satisfactorily treated by surgical methods. Little is known of the effect of radium on the majority of them. In some cases the diagnosis is doubtful, and it is then as well for the surgeon to remove them in view of the possibility of malignant disease being mistaken for a benign tumour. In some, however, where the surgeon is certain of his diagnosis, and where, for some reason, an operation is inadvisable, it would be well to try the effect of radium, especially if it could be applied from outside, as in the case of adenoma of the breast : in such cases one would expect to obtain remarkable results if the difference between the action on papilloma and epithelioma may be taken as any criterion.

Angeiomata

Deep angeiomata react well to radium rays. In order to close up the vessels, penetrating β-rays are the best on account of their action on the endothelium, and a filtration of 0·2–0·5 mm. of lead would be the most suitable. The dose will be large in order to

obtain a rapid result, but in the case of the enormous growths in the liver and elsewhere, sometimes seen, a moderate dose to any one portion must suffice on account of the general effects produced by a large number of these doses. If possible, the radium should be inserted into the growths.

Lymphangeiomata

These are treated in the same way as angeiomata, and even better results would be expected.

Uterine Fibromyoma

Here the action on the ovaries and the blood vessels partly accounts for the retrogression of the tumours. Chéron [1] claims the method as so successful that it is one to be used not as an exception but as a routine, on account of its certainty, simplicity, and innocuousness. He introduces a silver tube, 0·5 mm. thick, containing the radium, into the uterine cavity, taking special care that it acts upon the cervix; and if the fibroids are large, he, in addition, uses the radium externally on the skin. By this means he causes the menopause to supervene, after which, if the tumour retrogresses, he does not use any further treatment; but if it remains stationary or increases, he goes on with treatment. He claims—

1. That hæmorrhage is always improved, even when curetting has failed.

[1] "De la Radiumthérap'e des fibromes uterins," *Arch. d'électr. méd.*, Bordeaux, 1911, tome xix. pp. 353–363.

2. That pain is relieved—
   (*a*) By producing the menopause and stopping the catamenia;
   (*b*) By the decongestive action of the radium.

3. That great improvement in general health is obtained owing to the cessation of the hæmorrhage, while hardly any of the ordinary troubles of the menopause occur.

4. That retrogression of the tumour takes place, partly from the action of the radium on the ovaries, but also probably from its effect on the blood-vessels.

He gives the following as contra-indications :—

1. Inflammation of the adnexa or acute metritis, unless this be cured first.

2. Acute anæmia and bad flooding, in which case there is no time for the treatment to act.

3. Fibrous polypus and fibroids causing pressure.

4. Increase in size of the tumours notwithstanding the treatment.

5. Fibroids undergoing malignant degeneration but still operable.

Large doses are used with moderate filtration, and it seems possible that a great deal of the effect of radium is due to the destruction of the uterine mucosa with a sealing of its blood.vessels.

Metrorrhagia has also been treated successfully in the same way, and here again the result is probably due to a destruction of the mucous membrane of the uterus, and this will probably result in the uterus

becoming functionally useless, so that the treatment can only be adopted for severe cases. Gauss and Krönig,[1] however, while they confirm the beneficial results from γ-rays (they use mesothorium), deny that there is any destruction of the mucous membrane, even after large doses.

Chéron has obtained retrogression of fibromyomata after the menopause by subsequent irradiation. It is therefore evident that there is some action on the tumour apart from the ovarian effect and the changes induced by the resulting menopause, and we do not know what is the exact mechanism of this action—whether it is direct on the tumour cells or indirect by means of the blood-vessels.

Adenoma of the Prostate

A similar effect might be expected in other benign growths. In the enlarged prostates of old men little appears to have been done, but the prospects of benefit being obtained from radium treatment in this disease are good. The application may be made either by the rectum, by the urethra, or through the perineum, but in the first two situations great care must be taken not to cause burns.

Exopthalmic Goitre

Radium was first used in this affection by Abbé of New York, who introduced a radium tube into the thyroid gland. Great reduction in size was obtained with a disappearance of most of the symptoms. Wick-

[1] *Centralbl. f. Gynäk.*, Leipzig, 1913, Bd. xxxvii. No. 5.

ham and Degrais, Dominici and other observers have reported similar results by treating the disease externally, but the observations are not yet numerous. Considering the value of X-rays in this affection, and that radium usually acts similarly, but more powerfully, it seems obvious that a case has been made out for an extended trial of radium in exopthalmic goitre.

Malignant Growths

It is here that radium finds one of its greatest uses, as it supplies a method of dealing with a class of case which cannot be treated with equal success by any other method. It is true that only a small proportion of these patients get well, and a still smaller proportion remain well; but, at the stage at which these growths are submitted to radium-therapy, there is practically no hope of cure by any other method except perhaps X-rays, and this is not so successful as radium.[1] Even when radium fails to cause the disappearance of a growth, it often holds it in check and gives considerable relief from pain, diminishes the discharge, and may prevent the closing of a stricture of a tubular organ.

It is necessary to remember that, though malignant disease starts as a local growth, it is usually no longer so by the time it has become inoperable; further, the continued development of a neoplasm, even if local, diminishes the patient's resistance to the disease, so that the later the stage of the malady, the less responsive is it to the treatment. Then, again, in cases which are operable every surgeon knows how common recurrences are, even with the most complete operation. This, of

[1] The question of mesothorium rays is dealt with in the Appendix.

course, raises the question as to whether operable growths should ever be treated by radium. With a disease which, when untreated, is so universally fatal as this, it is impossible at present to recommend any patient to forgo the chance of surgical treatment, which is an old and tried method and at any rate gives a fair proportion of successful results; but we do insist that it should be combined with radium treatment in the forms of growth which react readily to this treatment. If only this prophylactic treatment were employed as a routine measure, we are convinced that many lives would be lengthened and many recurrences prevented. There is also a class of case in which the surgeon has notoriously bad results, and which, nevertheless, radium might benefit: in these it would be better to abandon the attempt at an operation and submit the patient to radium-therapy at once. In fact, some operating gynæcologists abroad go so far as to say that carcinoma of the cervix should be treated by radium and not by operation, even in early cases, and apparently their results in these comparatively early cases are far better than is possible when only inoperable cases are treated. Personally, we should like to see these cases treated by destruction of the growth by diathermy followed immediately by energetic radium treatment. If it is desired partially to remove an inoperable growth and then treat by radium, it is best not to use the knife for fear of opening up lymphatic channels and spreading the disease, but to employ some other destructive method, the best being diathermy.

Whatever type of malignant growth is being treated, attention must be paid to the general condition of the

patient, as, if this is bad, failure may result in an otherwise favourable case. It is also necessary to use every means available to improve the general health of such patients, fresh air, easily digestible and plentiful food, and so on.

Just as different healthy tissues react in divers ways and degrees to radium rays, so the various types of malignant growth respond very differently to these radiations: some are not destroyed by doses which would be detrimental to the healthy skin, while others completely disappear after having received only a small fraction of such a dose. Rapidity of development of the growth is no contra-indication to the treatment; in fact, except in some types of squamous epithelioma, the rapidly-growing forms often react more readily than the more slowly growing. In these former, however, the dissemination of the disease is more rapid, and even when the local growth disappears, recurrence in distant parts is the rule.

There is a possibility that some types of neoplasm may be stimulated to increased growth by insufficient radium application, and this seems more likely in growths which react badly. Like many other agents used in medicine, in which the effects of small quantities are exactly opposite to those produced by large ones, small doses of rays probably stimulate cell-reproduction while large doses depress it. Therefore when the less readily influenced types are treated extra care must be taken to give large doses.

The action of radium on new-growths is similar to, but not the same as, penetrating X-rays, and it is usually found that radium rays are the more effective, though in rare cases X-rays are said to have succeeded

where radium has failed : much more often growths, which have not improved under X-rays, have shown marked improvement when treated with radium. These remarks only apply to the best methods of treating these cases by either agent, namely, filtered rays and massive doses.

Types of Neoplasms most suitable for Radium Treatment

Sarcoma

The round-cell sarcoma, even in its very rapid and malignant forms, is undoubtedly one of the growths which reacts best of all to radium rays ; the actual size of the growth need not be feared, except with regard to the possibility of its having extended to a part not treated with the rays, but every attempt should be made to get rid of microscopical outlying deposits in any situation where there is a probability of their lodging. It will often, in a case of this nature, be advisable to make an opening into the growth and insert the radium tubes ; the tissues around the growth should also, as far as possible, be given as big a dose of the rays as they can stand without damage.

The objection, that insertion of radium tubes into a tumour may cause it to break through the skin, at once occurs. In a type of growth favourable to radium treatment, this does not happen, though it may in one which reacts badly or moderately. It is necessary, therefore, to consider the case carefully if this proceeding is to be adopted. Cutting into a tumour may favour lymphatic spread apart from opening a path to the surface. The risk of this

might possibly be minimised by using diathermic cauterisation instead of the knife. In some cases it will be possible to insert the radium into the tissues around the growth, care being taken to avoid a caustic dose as the tubes will be lying in healthy tissues. This method will find no extensive application for several reasons: several series of insertions will have to be made to reach the tissues on every side of the growth; if the tissues around the growth are free from disease, it is usually operable, and, finally, the advantage of the caustic dose to the main tumour-mass is lost.

In very large masses of round-cell sarcoma, such as lympho-sarcoma of the mediastinum and the glands in the neck, the quantities of radium available at present are insufficient, and though a large quantity of radium might produce some remarkable results in these cases they will generally have to be treated with X-rays, which are very effective, at any rate for a time.

The other types of sarcoma are not so uniform in their reaction to radium; some, especially of the spindle-celled variety, retrogress in a very satisfactory way, while others are very refractory. Of myeloma we have no experience; it will almost invariably be operable.

Lymphadenoma

This shows an even greater susceptibility to the radiations than lympho-sarcoma. It is unfortunately almost always generalised when it is discovered. We are strongly against the operative removal of this disease when it is localised in the neck, as it always recurs. If the patient were treated at this stage

with radium and X-rays he would stand a far better chance of recovering ; in fact, with thorough treatment which would include irradiation of the mediastinum and the other side of the neck, though apparently unaffected, his chances of getting well would be very good.

Epithelioma

On the whole, squamous epithelioma does not react well. This is most unfortunate, as it is usually superficial, and, when good results have been obtained, they are easily demonstrated and very striking. A false impression has thus been created as to the value of radium in this type : some epitheliomata, it is true, do give good results, notably those of the cervix, lip, and œsophagus, but the commonest form, the epithelioma of the tongue, is most refractory. Personally, we hold the view that it is very seldom justifiable to treat epithelioma of the tongue or of the vulva with radium, and if it is undertaken the patients or their friends must clearly understand the small chance it offers of doing good. Epithelioma of the floor of the mouth, the buccal mucous membrane, the tonsil, the fauces, the palate, the pharynx or the larynx, is not so refractory, and the treatment may be adopted with a fair prospect of giving relief; in occasional cases complete retrogression is seen. The same growth in the skin gives similar results, but the spread to the lymphatic glands and other parts is earlier and less tractable. Glandular involvement is not an absolute contra-indication in these cases, though it seriously prejudices the chances of a cure ; however, many glandular deposits have been caused to disappear by

radium, and even when this does not occur, to have the primary growth healed may render the patient considerably more comfortable.

In epithelioma of the lip, cervix, and œsophagus the results are better, though usually the patients only come for radio-therapy in a very late stage. Cervix growths vary very much, sometimes shrinking up to a remarkable extent, but metastases in the abdominal glands and liver usually prevent a successful result. Œsophageal growths are generally of the squamous type, and very considerable relief can be given by preventing stenosis, and relieving pain; they would seem to afford a great opening for radium treatment, as they are almost always inoperable, even in the earliest stages; unfortunately they are hardly ever discovered at this period and are generally far advanced before they produce symptoms. Local improvement is usually obtained, though the growth does not react readily, and the mediastinal ramifications cannot be expected to be influenced. We have seen an extensive ulcerating carcinoma about three inches long in the lower part of the œsophagus, which cicatrised and which was well three years after treatment. Another œsophageal cancer which the author treated healed up completely. The patient disappeared and was so well that he refused to come up for further examination or treatment. Four years later, however, he returned to hospital, and died from hæmorrhage from a recurrence, which was found post-mortem in the mediastinal glands which had opened a small intercostal branch of the aorta. The primary growth, even at this time, had not spread much beyond the muscular coats of the œsophagus, and contained a very large quantity of fibrous tissue.

It would appear that the treatment had kept this patient alive long enough to allow recurrences from the mediastinal glands to ulcerate into the œsophagus, a most unusual occurrence.

In the arytenoid region favourable results are sometimes obtained, but the possibility of an application to this part being followed by pneumonia in feeble subjects must not be overlooked. In a case treated in conjunction with Dr. William Hill, the growth and glands disappeared, and the patient remained free for more than a year, when the disease recurred in the post-cricoidal region and the patient did not present himself for treatment until the disease was too far advanced.

In the whole of this class of tumour the possibility of surgical or diathermic removal after the radium has reduced it in size must be considered, even if it was originally impossible. It will, unfortunately, often be found, in such a case, that the fibrous tissue formed after the shrinking of the growth, and possibly due to the radium action, will cause serious difficulties to complete surgical removal. Diathermy may also be used to get rid of much of the growth before the radium is used, and this combination has much to recommend it.

Carcinoma

Glandular carcinoma or adeno-carcinoma forms a very large class, the disease as it affects the breast being the commonest new-growth met with. On the whole, glandular carcinomata, whether spheroidal or columnar-celled, react well to radium, though they vary a good deal. Adeno-carcinoma of the breast

usually responds, but it only becomes inoperable at a very late stage of the disease, generally after the surgeon has operated several times, and at this period the disease has usually spread far and wide, infecting the mediastinum, the liver, and other parts. If there are multiple recurrences and indications or likelihood of infection of the mediastinum, it is better to use filtered X-rays than radium, as, although the former do not have so good an effect in destroying the cancer tissue, the great mass of rays that can be poured into the body can give large doses to more distant parts, and have a greater effect than the small doses of radium rays that can be made to reach these parts. This statement may have to be modified as soon as sufficient radium is available ; for instance, when we have a large quantity we shall probably be able to saturate the whole of the chest with an efficient dose of radium rays, by using our radium at some distance from the skin (see Chapter IV., p. 60), and by using the cross-fire method, that is applying the radium from the front, back, and side. In the form of breast carcinoma in which there is a flat, open ulcer with little tumour formation beneath it, the healing of the ulcer can usually be obtained ; though these cases are common, the author has, unfortunately, not come across any to treat with radium, but successes in this disease have been obtained by other radium-therapists.[1] The rapidly-growing cancer of the breast, except in young people, reacts more readily to radium than these slowly-growing forms, but here again radium treatment is severely handicapped by the late stage in which the disease is encountered.

[1] Dominici, Wickham and Degrais, etc.

Carcinoma of the rectum, a columnar-celled growth, varies a good deal in its behaviour to the radiations; the cases which do well are of the type which produce large fungating masses in the lumen but show comparatively little tendency to spread deeply. This, again, is a rapidly-growing tumour. The infiltrating variety usually improves under radium treatment but not to the same extent, and, unfortunately, inoperable forms of it are much commoner.

A recurrence, which had the most malignant characteristics the author has ever seen, and which showed a remarkable result, was called by some pathologists glandular carcinoma and by others endothelioma. The primary growth occurred in the cheek, an apparently innocent tumour which had existed for many years. It took on malignant characteristics, and was thoroughly removed, but recurred a month later and within a fortnight had grown to enormous dimensions. The insertion of radium tubes into this mass was followed by its complete disappearance, and after prophylactic treatment the patient remained well for over a year: a recurrence in the brain then, unfortunately, became evident and caused her death a month or two later. The recurrence was not treated with radium.

Carcinoma of the body of the uterus or a recurrence after removal of such a growth is readily influenced by radium. Chéron and Rubens Duval have reported a case at the French Académie in which the patient died of intercurrent disease fifteen months after the treatment: at the autopsy it was impossible to find in the cicatrix any evidence of malignant cells.

Carcinoma of the stomach would probably react readily, but though such cases have been treated via

the œsophagus, it would generally be necessary to make the growth accessible by means of an operation, fixing it to a wound in the front abdominal wall. The same may be said of growths in the intestine, but these tumours, as those of the stomach, will, if inoperable, probably have affected the glands far and wide, and treatment for relief will not be advisable on account of their inaccessibility.

It will be noticed that the types of growth, speaking generally, which are most favourable for radium treatment are the soft vascular rapidly-growing neoplasms, just the forms which are the least satisfactory from the surgical point of view, except in the case of the rectum and possibly a few other situations.

The factors, then, that influence the choice of cases are—

1. The nature of the growth.
2. Its position and size.
3. The general condition of the patient.

Methods of treating Malignant Growths by Radium

French teaching revolutionised our methods of using radium in malignant disease, the chief improvement effected being the introduction of metallic filters to screen off the less penetrating rays: the use of large quantities was also laid stress on, but large amounts had previously been used in America.

No malignant growth should be treated without using a filter of at least 0·5 mm. of silver, which corresponds to about 0·3 mm. of lead and 0·2 mm. of platinum. It is true that some tumours can be removed by

unfiltered rays, but, even in them, the action of filtered rays causes less inflammation and little or no necrosis, and altogether is more comfortable for the patient even if the growth is on the surface. A screen of 0·5 mm. of platinum gives very satisfactory results with rodent ulcers, but for more malignant growths 2 mm. of platinum should be preferred. It may be that each type of growth requires a special amount of filtration just suitable to it, but our knowledge is not sufficiently advanced to determine whether this is the case. When the radium tubes can be inserted into the tumour, or into the tissues around it, this should be done, and if the growth reacts readily and rigid aseptic precautions are employed, there is little likelihood of a sinus remaining after the treatment. In refractory growths, on the other hand, where a caustic dose has been employed a sinus may result, forming either at once or in the reaction period. As well as the insertion into the growth it is necessary to flood with radium rays the whole area which may have become infected with the tumour cells, even if there is no macroscopical evidence of this having occurred. Thus, in a carcinoma, care is taken to treat the lymphatic glands in the region which provides drainage for the affected part : again, in a melanotic sarcoma the thorax should be treated, owing to the frequency with which deposits in the lungs occur with this form, and, as insufficient quantities of radium will usually be available for this purpose, X-rays must be used. The secret of success will lie in early, persistent and radical treatment, but burns must be most sedulously avoided, as not only are they very difficult to heal and extremely painful but they break

down again with very small doses of the rays: they therefore prevent treatment just when it is most necessary. The commonest cause of a burn is the radium accidentally coming into contact with the healthy skin or mucous membrane and remaining there for some time when an attempt is being made to give a caustic dose to an ulcerated growth: this is especially likely to occur high up in the rectum owing to the difficulty of controlling the exact position of the tubes.

It will often happen that for various reasons the radium cannot be inserted into a growth or that it is desired to treat a lymphatic gland area from outside the skin. A pad of lint is then used to separate the radium from the skin (see Chapter I.). If the tumour projects, the radium is applied on all sides so that the rays cross, but whether with a given quantity of radium it is better to divide this and apply it simultaneously in different directions or to use the whole successively over the various places, is not determined. The tumours submitted for radium treatment are not usually amenable to the "cross-fire" method, as it is called, unless one tube is actually inserted into the growth and the others used outside, and then it seems preferable to insert all the tubes into the growth if possible, when, of course, a cross-fire is obtained inside part of it.

Special methods of treatment will be found in Chapter IV.

After-Treatment

A skin area that has been treated should be kept dry, and no medicament should be applied to it unless

there is any irritation or inflammation, in which case a powder of zinc oxide and starch (B.P.) should be prescribed. Parts of the skin continually moist, such as around the anus, are liable to more severe reactions than dry portions. On no account should any ointments be used, as they may convert an erythema into an ulceration. If the action of the radium has gone too far and there is a burn, every effort should be made to keep this dry with large quantities of the above powder, and only if there is acute pain that requires temporary relief should cocaine or novocaine be used. No stimulant dressing is allowable. In the œsophagus, adrenalin gives relief in the reaction period.

If an ulcer has been treated, the crusts which form on it should not be removed ; an endeavour is made to obtain a dry scab under which the ulcer will heal. The scab usually falls off five or six weeks after the treatment, or may be removed at this time to permit of a further application.

On mucous membranes or skin surfaces which cannot be kept dry, quite a small dose will produce what is often misnamed ulceration ; a whitish semi-translucent membrane forms on the surface, firmly adherent to the subjacent tissue, an attempt to remove it causing bleeding. If a surface has received the same dose all over, this film disappears almost simultaneously from all parts of it, and not from the edges, as it would if there really were ulceration. Larger doses will, of course, undoubtedly cause ulceration and sloughing. The membrane above referred to is best left alone, and any irritants kept away from it. The vagina seems much less susceptible to the rays than the other mucous membranes, and

the tongue and mucous membrane of the cheeks are especially sensitive.

It is as well to warn patients that they may expect some reaction, which may be painful, two or three weeks after the application.

It appears to be advisable to use as large a quantity of radium as possible, not only in order to treat the whole of the affected area within a reasonable time and to enable one to give an efficient dose to deeper deposits, but because larger quantities, although used for a proportionately shorter time, appear to be more effective than smaller amounts. A rough working basis is to take the product of the time and the mass of radium in equilibrium as the dose, and though this formula approaches the truth the mass appears to be somewhat the more important factor. For example, 100 mgrms. of radium bromide applied for one hour is more effective than 10 mgrms. applied for ten hours. In the treatment of rodent ulcer quite small quantities may often be used, but in the truly malignant tumours the quantity should not be less than 50 mgrms. of radium bromide (26·8 mgrms. metallic radium), and it is inadvisable to use less than 100 mgrms. of the bromide.

The dose should be so regulated that the healthy tissues only receive enough to cause a slight inflammatory reaction to follow without any ulceration, and such a dose will destroy any but the most refractory growth cell. The action depends upon the fact that the same dose that will have no effect on healthy cells will destroy growth cells. This is proved by a deep-seated tumour being often destroyed without the skin over it, which receives

a much larger dose of rays, being damaged. In rodent ulcer, again, a dose which does no harm to the healthy skin is sufficient to cause the growth to disappear and heal up the ulcer. No care need be taken to limit the action on the diseased cells themselves, and they are frequently given many times the dose that would be sufficient to cause ulceration in the skin. This is referred to as a caustic dose, and in a susceptible growth causes no sloughing; in a refractory tumour, however, sloughing may follow such treatment. When the radium is inserted into a tumour, the time of the application should be so regulated that the growing surface just receives a full dose and no more; that is to say, that the dose is pushed to the limit which will just fail to damage healthy structures.

The cardinal principles, then, in the treatment of malignant disease are—

1. Treat thoroughly the whole tumour and the site of any likely metastases.
2. Adequately filter the rays.
3. Use as much radium as possible.
4. Give maximal doses.

The application is repeated about every six weeks until all trace of the tumour has disappeared. *At least* two prophylactic doses are then given at intervals of two months, and the patient kept under careful observation for some years.

Prophylactic Treatment

This will be given on similar lines to the curative treatment, but must be strictly limited to the non-

caustic doses. Two treatments are given at an interval of six weeks, the first preferably at the time of the operation, the tubes being left in the wound, and the second external. A third dose is given two months after the second.

The indications for prophylactic treatment are imperative in a readily reacting growth, and even a refractory growth may be treated, as it has been found that a small neoplasm will often disappear where a large one of the same type would not be benefited.

Far too little attention is given by surgeons to this powerful weapon for prevention of recurrence, more particularly so, as the cases in which it is most useful are those most liable to recur.

Results

It is evident that most of the cases of malignant growths submitted to the radium-therapist will be incurable to any form of treatment, especially as they are all inoperable and are usually extremely advanced cases. With rodent ulcer it is otherwise—this is usually readily cured even when other treatments, X-rays included, have failed, and it is very unusual, so far as the author's experience goes at present, to get recurrence.

Notwithstanding the hopeless nature of inoperable malignant cases, radium will in 10 to 15 per cent. cause a disappearance of the local growth, and some patients have remained free from recurrence for several years. Unfortunately, disappearance of the main growth has little or no effect on secondary deposits, and therefore, if these exist, unless they are also treated, a metastatic

recurrence will sooner or later become manifest. It is quite possible that the prolongation of the patient's life may allow metastases to become evident in situations in which they would ordinarily not have time to develop.

Even when a complete disappearance of the growth is not obtained, the improvement is usually very manifest. A notable diminution often takes place in the size of the growth, pain is much lessened or entirely removed, while fœtid discharges disappear and hæmorrhage ceases in the majority of cases. This relief from pain seems to be more than can be accounted for merely by a retrogression of the growth or by relief of pressure caused by it, and the direct analgæsic action of radium on the nerves probably has something to do with it. In one of our cases, relief from months of violent pain was complete in forty-eight hours from the commencement of the application, although the growth was only slightly diminished by the treatment. By carefully selecting only suitable cases extraordinarily good results might be obtained, but the occasional success that sometimes occurs in apparently the most hopeless cases prevents the selection to a large extent and leads to a number of cases being treated in which one cannot expect more than improvement. Further, so much relief can be given in cases which it is impossible to cure that these too will form a great factor in spoiling the statistics of the treatment.

It is often observed that the first treatment and earlier treatments have more effect than later ones in the same case. A possible reason for this has already been alluded to, namely, diminution of the patient's

resistance to the disease. It has also been suggested that the improvement is due to diminution of inflammatory changes round the growth. Clinical experience and microscopical study do not bear this out.

When a growth disappears, it may still leave trouble in its wake. For instance, carcinoma of the rectum may leave a troublesome stricture after it has disappeared; dilatation must then be used to keep this open. Similarly, in the œsophagus a hard fibrous stricture may be left after all trace of malignant growth has disappeared. On the other hand, in superficial conditions remarkably little scarring is seen after the treatment.

For many years it will be impossible to determine the permanency of the results. The longest case the author has healed has now been well over four years, and he knows of others who have been well over five years. As with any other treatment of malignant disease, the chance of recurrence is great and the recurrence may or may not be amenable to radium treatment.

In the rare event of two types of malignant disease occurring in the same patient, one may respond while the other does not.

Diseases of the Blood and Lymphatic System

Leukæmia will probably give good results when larger amounts of radium are available for use. In an early case of lymphatic leukæmia in which the spleen only was treated by the author some years ago with only 50 mgrms. of radium bromide, notable improvement was seen. Not only was the leucocyte count reduced from

40,000 to about 8000, but the proportion of polymorpho-nuclear leucocytes was raised from 0·5 per cent. to about 30 per cent. The improvement in this case persisted for some years, but the patient was not submitted to further treatment.

Inflammatory Conditions

The beneficial action of radium rays in inflammations cannot be explained by their action on bacteria, as, in the doses given and using β and γ-rays these would have very little effect on the micro-organisms. The effect appears to be due rather to the fact that they excite a process in the healthy tissue which is inimical to the germs.

Though not often used for this purpose, there is no doubt that radium is very useful in getting rid of chronic inflammatory conditions. The principles of treatment are the same as for malignant growths, with the exception that considerably smaller doses will be needed.

In tuberculosis of the glands of the neck it has proved very useful. In cases which have not broken down the results are very good, but probably not better than with filtered X-rays. When, however, a sinus has formed this seems to invite the insertion of a radium tube into it, an invitation not by any means to be despised.

There does not appear to be any record of the use of radium in other tuberculous deposits.

In tertiary syphilis it has proved useful.

In gonorrhœal arthritis and gonorrhœal orchitis radium irradiation has been very successful even in

the acute stage, and this is probably due to special susceptibility of the gonococcus to the rays.

In rheumatoid arthritis the direct action of the rays on the affected joints has been shown by Soupault and then by Dominici and Gy to relieve the pain and diminish the stiffness in some cases but not in others. In gout irradiation has also proved successful but is not so effective as internal administration of the emanation.

Other inflammatory conditions have been treated by hypodermic, intravenous, intrapulmonary or intradural injection of radium salts, but the number of observations is insufficient to draw any conclusions. Maladies as various as pneumonia, meningitis, septicæmia, acute myelitis and enteric fever have been treated by this method (Dominici and Chevrier).

Diseases of the Eyes

Radium rays have proved very useful in some diseases of the eye. They act in the first place as an analgæsic in painful affections, and secondly as an agent causing absorption of exudates and retrogression of inflammations. Darier first called attention to these actions, and Mackenzie Davidson considerably extended the scope of the ophthalmological applications of radium.

The analgæsic action in such affections as choroiditis, iritis and ocular rheumatism is most marked and is often followed by a subsidence of the disease. In Darier's cases small quantities of radium in a very weak form were used; in Mackenzie Davidson's, glass tubes containing nearly pure salts.

It has been found of great use in spring catarrh, trachoma and other chronic inflammatory conditions of the conjunctiva. Absorption of corneal opacities after radium treatment has also been reported.

Diseases of the Ears

We have not yet heard of or seen the employment of radium for disorders of hearing, but it seems possible that it would do good in deafness due to sclerotic conditions in the middle ear owing to its power of causing absorption of sclerotic tissue.

Nerve Diseases

The action of radium as an analgæsic has been insisted on already, and it will be realised therefore that it is of great value in some forms of neuritis and some neuralgias. In central organic lesions it will seldom have any effect, but in one disease, syringomyelia, its action is very marked. The application is made by applying filtered rays to the region of the spine which is affected.

In sclerosis of the spinal cord it seems too much to expect any good effect, but owing to the action of radium on pathological fibrous tissue it might be worth while investigating its action in some of these diseases. It might also be employed in the lightning pains of tabes.

. . . . . .

In conclusion we may say that several years' experience with radium has convinced us that its uses will be considerably increased in the future, but only

along certain lines, and its employment will be strictly limited to the class of case for which it is suitable. In some instances it will stand supreme as the best treatment, while in others it will be a valuable alternative to other therapeutic methods.

APPENDIX

OTHER RADIO-ACTIVE SUBSTANCES

Uranium

This metal is the parent of radium and probably of actinium, and has a slight radio-activity. The table of its decay products is as follows :

	Time to fall to half value.	Radiations.
Uranium 1 . .	5×10^9 years	α
Uranium 2 . .	10^6 ,, (?)	α
*(Uranium Y .	1·5 days	β)
Uranium X . .	24·6 ,,	β & γ
Ionium . . .	2×10^5 years (?)	α
Radium . .	2000 years	α

* Branch product.

Where actinium separates from the parent tree is not known.

Uranium salts have been used in the treatment of rodent ulcer, and successes have been claimed. Pitchblende is a mineral from which radium is extracted and owes its activity chiefly to its content of this metal; it nevertheless consists chiefly of uranium compounds and its therapeutic effects may be due partly to these. It has been used where a long-continued small dose of rays is required, as in port-wine

marks. It has also been used in recurrent carcinoma, but is not so satisfactory as massive doses of rays from radium.

Thorium, Mesothorium, Etc.

Thorium, the compounds of which are largely used in the manufacture of incandescent gas mantles, is, like radium, a substance which decays into a series of radio-active products some of which are far more active than the parent substance. Of these, mesothorium 2 is many times as active as radium, supposing both to be in equilibrium with their decay products. Though it has hitherto not been possible to get a greater proportion of mesothorium than 1 per cent. mixed with radium, from which it cannot be separated, this mixture has nevertheless a radio-activity four times as great as that of the radium alone.

The series of thorium decay products is as follows :

	Time to fall to half value.	Radiations.
Thorium . . .	$1{\cdot}3 \times 10^{10}$ years	α
Mesothorium 1 . .	5·5 „	no rays
Mesothorium 2 . .	6·2 hours	β & γ
Radiothorium . .	2 years	α
Thorium X . .	3·65 days	α & β
Emanation . .	54 seconds	α
Thorium A . .	0·14 „	α
„ B . .	10·6 hours	β & γ
„ C . .	60 minutes	α & β
*(„ C^2 . .	very short	α)
„ D . .	3·1 minutes	β & γ

* Branch product.

It is seen that the mesothorium 1 is an inactive product, but it soon forms mesothorium 2, so that the activity gradually rises, a maximum being reached in 4·6 years and the activity then is about double that due to mesothorium 2 alone, owing to the formation of radiothorium and other decay products. The radio-activity of the strongest mixed product manufactured by O. Knöfler & Co., Berlin (1 per cent. mesothorium, 99 per cent. radium), rises in 3·2 years to 46 per cent. above its original strength and falls again to this in about ten years. When all the mesothorium has disappeared the final product, which is radium, has an activity about 25 per cent. of that of the original mixture. At its greatest activity the mixture is about six times as active as radium alone. To put it another way; to obtain the same activity as radium one-sixth the weight of the mixture is necessary. Its rate of change is slow and can be accurately calculated. The β- and γ-rays from mesothorium 2 are somewhat less penetrating than those from radium C, while the β-rays from thorium B are considerably less penetrating, but the rays from thorium D have about the same penetration as the β- and γ-rays of radium C, and the α-particles from thorium C^2 are about the most penetrating α-rays known.

Theoretically, then, we should expect the same results from mesothorium rays as from radium rays applied externally, and the work on the subject up to the present rather bears out this view, though it is difficult to determine exactly how much of the result is due to the radium rays in the mesothorium mixture. Administered internally, all the thorium

salts and decay products appear, apart from any radio-active effect, to be very poisonous—much more so than radium. Great caution is therefore to be exercised in their administration, especially as fatal results have already been reported from the injection of thorium X.

Czerny and Caan[1] report that a more intense superficial reaction is obtained than with radium, if light filters or none at all are used, and this has a very short latent period, averaging forty-eight hours, and an ulceration occurs which, however, heals rapidly. It is very difficult to understand the results of these investigators, for they find that lymphosarcoma in eight cases proved absolutely refractory. Not only should this not be so from analogy with radium, but this growth usually reacts so readily and to such small doses that the radium in the mesothorium preparation should by its own rays have caused some beneficial result. It is also stated in their paper that nodules of carcinoma only disappeared, as a rule, two or three months after the application. If these results are confirmed—and until this occurs they must be accepted with the utmost reserve—they indicate that the similarity of the mesothorium rays to radium in their physical properties does not hold in their medical applications.

Other observers have reported beneficial results in lupus, and it may have some advantages over radium and X-rays in this disease.

We have seen this treatment employed in Germany, and have been surprised to note the extraordinary amount of general symptoms produced *at the time* of

[1] *München. med. Wchnschr.*, April 2, 1912, Bd. lix. (14), S. 737.

the application, so much, in some cases, that the mesothorium apparatus had to be removed before the treatment was concluded. Notwithstanding assurances to the contrary, we suspect the escape of minute quantities of the salt, more especially as we were informed that the strength of the apparatus varied considerably from day to day for no apparent reason.

Thorium emanation inhalations have been employed for phthisis, but, we believe, with scant success.

Thorium X has been used internally by the mouth, by hypodermic or intravenous injection, and in other ways, for the same class of diseases as radium emanation, but it is so far too early to speak of results.

Actinium, a metal which, like radium, appears to be a descendant of uranium, has the following family :—

	Time to fall to half value.	Radiations.
Actinium . . .	?	No rays
Radioactinium . .	19·5 days	α & β
Actinium X . .	10·2 „	α
Emanation . .	3·9 seconds	α
Actinium A . .	·002 „	α
„ B . .	36 minutes	slow β
„ C . .	2·1 „	α
„ D . .	4·71 „	β & γ

The greater part of the penetrating β- and γ-radiation arises from actinium D, the β-rays from which are half absorbed by 0·24 mm. aluminium.

We are not aware of any conditions for which this substance has been proved of therapeutic value, but very little work appears to have been done with it.

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